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Recent Advances in the Chemistry of Macroline, Sarpagine and Ajmaline-related Indole Alkaloids

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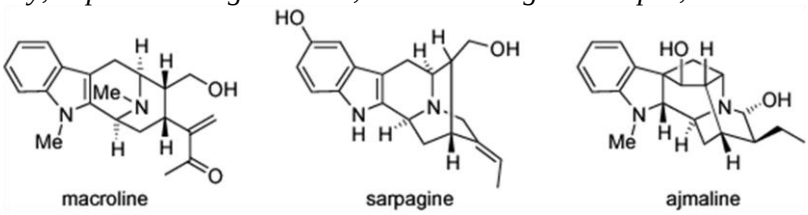

Pergamon

TETRAHEDRON

Recent Advances in the Chemistry of Macroline, Sarpagine and Ajmaline-related Indole Alkaloids

Simon E. Lewis*

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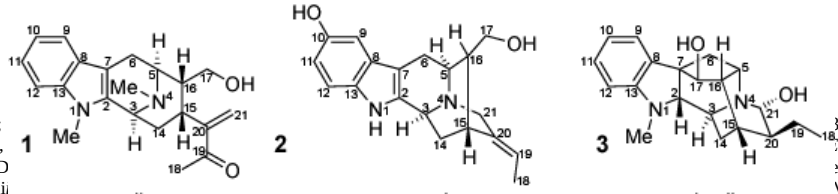
Contents



Abbreviations list: Ac, acetyl; [illegible].3.1]nonane; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bu, butyl; Bz, [illegible])-dibenzylideneacetone; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; D[illegible]ess; DHQ, dihydroquinine; DHQD, dihydroquinidine; DIBAL-H, di[illegible]V-dimethylformamide; DMP, Dess–Martin periodinane; DMPU, *N*,[illegible]io; *E*, entgegen; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; ee, enantiomeric excess; Et, ethyl; h, hours; IBX, 2-iodoxybenzoic acid; IMDA, intramolecular Diels–Alder; LDA, lithium di*iso*propylamide; Me, methyl; min, minutes; N, normal; NBS, *N*-bromosuccinimide; NMO, *N*-methylmorpholine-*N*-oxide; Np, naphthalenide; *o*-Ns, *ortho*-nitrophenylsulfonyl; Ph, phenyl; PHAL, phthalazine; *p*-TSA, *para*-toluenesulfonic acid; py, pyridine; rt, room temperature; Sia_2BH, di*iso*amylborane; SM, starting material; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TES, triethylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TIPS, tri*iso*propylsilyl; TMS, trimethylsilyl; TPAP, tetrapropylammonium perruthenate; Ts, *para*-toluenesulfonyl; *Z*, zusammen.

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Scheme 1.

1. Introduction and Scope

A huge variety of indole alkaloids are known,[1-7] many of which have been submitted to total synthesis. This review concerns the chemistry of indole alkaloids related to macroline **1**, sarpagine **2** and ajmaline **3**. The structures of these three species are shown in Scheme 1.

The skeletal numbering shown is the biogenetic numbering proposed[8] by LeMen and Taylor and is used throughout this review. It may be seen that there is significant structural similarity between the three compounds. All possess an indole-annulated azabicyclo[3.3.1] structure and various efforts towards this structural motif are detailed below. Macroline-related alkaloids are defined as those having the same skeletal connectivity as macroline. They crucially do not possess an N4-C21 linkage. Sarpagine-related alkaloids are defined as those having the same skeletal connectivity as sarpagine, specifically with an N4-C21 linkage and the C16-(*R*) configuration shown. Ajmaline-related alkaloids are defined as those having the same skeletal connectivity as ajmaline, also with an N4-C21 linkage but with the C16-(*S*) configuration epimeric to that of sarpagine as shown. Alkaloids with a quaternary C16 are known and are included herein. There also may or may not be a C7-C17 linkage, the quaternary C7 implied thus rendering the C2-C7 bond saturated. Additionally, the compounds under consideration may or may not be N1- and N4-substituted and may or may not possess indole ring oxygenation. Bis(indole) alkaloids in which one or both of the subunits consist of a macroline/sarpagine/ajmaline indole base are also included in this review.

It must be noted that, unlike ajmaline and sarpagine, macroline has not been isolated from natural sources. Many macroline-related alkaloids have, however, been isolated and it is believed that macroline, or an equivalent, is a likely biosynthetic precursor of various sarpagine alkaloids.

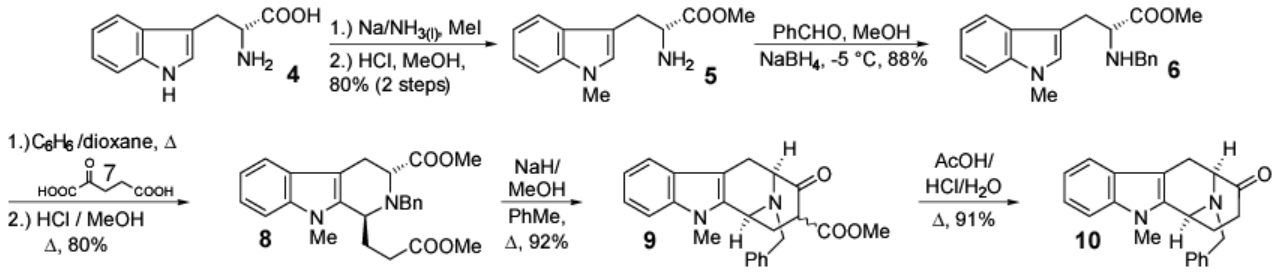
Scheme 2.

One can envisage the relationship in a synthetic sense, with 1,2- or 1,4- addition of N4 to C19 or C21, respectively, providing access to the sarpagan skeleton. Such a synthetic strategy has been employed in some of the total syntheses detailed herein. The reverse transformation may also be envisaged – quaternisation of N4, followed by Hofmann elimination (provided C20 has an appropriate hydrogen, e.g. in ajmaline) resulting in N4-C bond scission. This strategy has also been adopted in total synthesis, as will be seen, and interconversions of this nature are important in structural elucidation and stereochemical correlation.

The field of macroline, sarpagine and ajmaline-related alkaloids was reviewed extensively by Cook[9,10] in 1993 and 1994 and again by Lounasmaa[11,12] in 1999 and 2001. As well as detailing reported synthetic endeavours relevant to the field, these excellent reviews give a comprehensive account of the species from which these alkaloids have been isolated (mostly genera *Rauvolfia* and *Alstonia*) and an overview of their biology, pharmacology, spectroscopic characteristics and proposals for their biosyntheses. Only chemistry of particular relevance, as well as that reported subsequent to these prior reviews or that not covered therein, is included here.

2. Cook's Syntheses

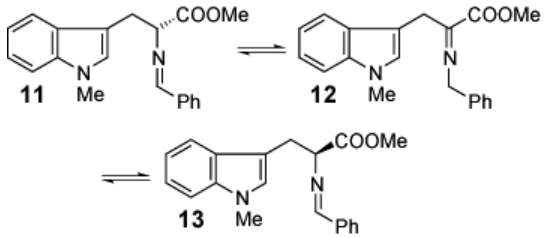
Cook and co-workers have published extensively in the area of indole alkaloids and, in the last decade, have reported the partial and total syntheses of more than 40 macroline/sarpagine/ajmaline-related alkaloids, as well as bis(indole) alkaloids and related degradation products. These syntheses are detailed in this section and are grouped by the methodology used, as opposed to the final targets in question.



2.1. The tetracyclic ketone

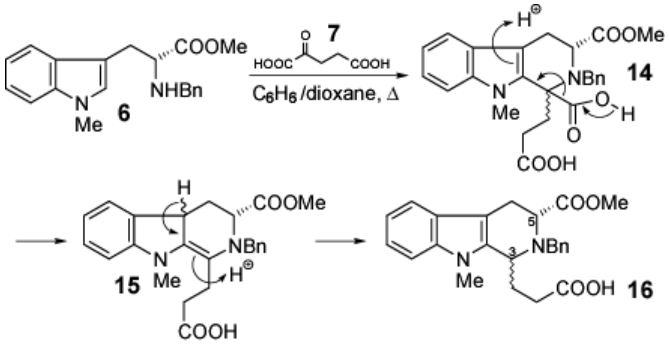
Fundamental to Cook's syntheses is the tetracyclic ketone intermediate **10**. Its synthesis has been reviewed before,[9,11] but will be detailed here also due to its relevance to the following sections. The overview of the synthesis is shown in Scheme 2.

The synthesis outlined above, whilst only seven steps, hasbeen the subject of extensive study and optimisation.[13] The individual steps merit consideration in detail. Starting from unnatural D-tryptophan **4**, N1-methylation and esterification were routine. The reductive amination to protect N4, however, required careful control. After stirring **5** with benzaldehyde for 2 h at room temperature to form the imine, sodium borohydride was added at –5 °C and allowed to react for 3 h. Longer reaction times or higher reaction temperatures led to erosion of the *ee* of **11** by imine isomerisation to **13** *via* **12** (Scheme 3).



Scheme 3.

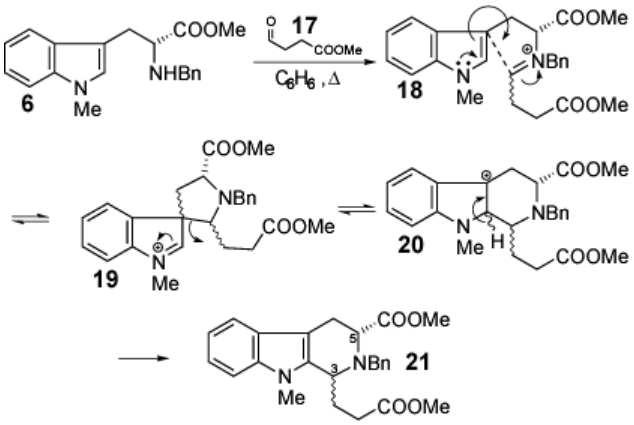
The Pictet–Spengler condensation (and subsequent esterification) shown in Scheme 2 is represented as affording solely the C3,C5-*trans* tetrahydro-β-carboline **8**. In fact a more complex series of events was occurring. As shown in Scheme 4, the initial Pictet–Spengler cyclisation proceeded to give a diastereoisomeric mixture of tetrahydro-β-carboline diacids **14**. These underwent decarboxylation as shown and it was therefore the protonation upon rearrangement of intermediate **15** that determined the diastereoisomeric ratio in the product, not the inherent selectivity in the Pictet–Spengler reaction.



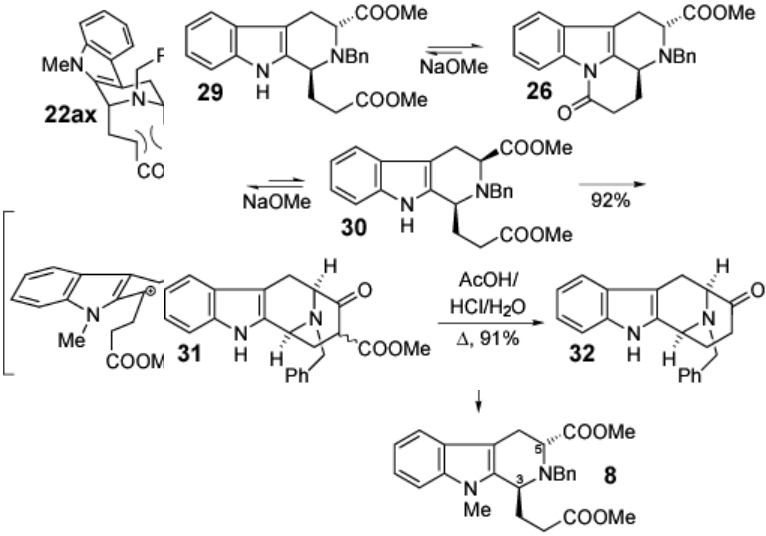
Scheme 4.

If the tetrahydro-β-carboline monoacid intermediates **16** were isolated, the diastereoisomeric ratio was found to be C3,C5-*cis*:*trans*=42:58. Alternatively, if methyl 3-formylpropionate **17** was used in place of 2-ketoglutaric acid **7**, the diastereoisomeric ratio in **21** was found to be C3,C5-*cis*:*trans*=28:72 (Scheme 5). This enhanced diastereoisomeric ratio was observed due to the lack of a post-cyclative decarboxylation step; in this instance, the ratio is a true representation of the inherent selectivity of the Pictet–Spengler cyclisation.

Scheme 5.



Whilst the reaction of methyl 3-formylpropionate **17** with **6** increased the diastereoselectivity in the formation of **21** *via* **18**-**20**, total selectivity was desired in order that tedious chromatography might be avoided and the sequence might be executed on a large scale. This was achieved by acid-catalysed isomerisation of the C3,C5-*cis* isomer to the more stable C3,C5-*trans* isomer, simply by treating the diastereoisomeric mixture **16** or **21** with methanolic HCl (for **16,** this also effected esterification). The isomerisation of **22** is thought to proceed *via* a C3-N4 bond cleavage and formation of stabilised C3 cation **23** (Scheme 6).



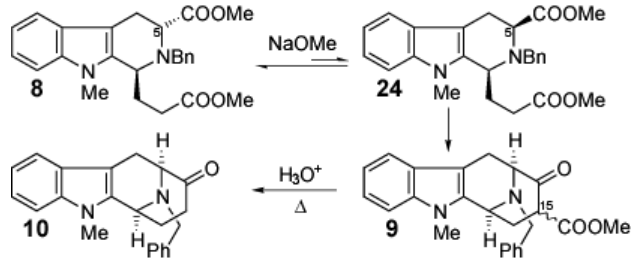
Scheme 6.

With pure **8** in hand, Dieckmann condensation to the tetracyclic system **9** was effected with sodium methoxide. The C3,C5-*trans*-configured tetrahydro-β-carboline **8** is unable to attain a conformation suitable for cyclisation, and so base-induced epimerisation of C5 must occur prior to cyclisation. Whilst the *cis* tetrahydro-β-carboline **24** is the less stable diastereoisomer (as established in Scheme 6), the small amount formed is irreversibly transformed to the tetracycle, the equilibrium then replenishes the amount of **24** present and so all material is eventually transformed into tetracycle **9** (Scheme 7). The epimerisation prior to Dieckmann cyclisation is the reason Cook's synthesis commences with the unnatural amino acid antipode. This

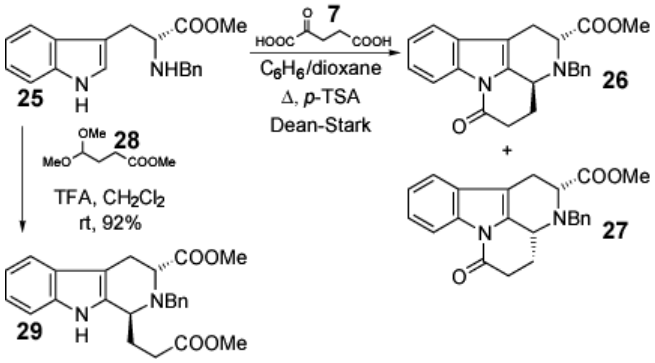
(incorrect) initial C5 configuration induces the correct C3 configuration which, in turn, induces complete epimerisation at C5 to the correct configuration.

Scheme 7.

The uncontrolled configuration of C15 in **9** is of no consequence as acid-induced decarboxylation leads to key tetracycle **10** (7 steps from D-tryptophan, 47% overall yield). Cook's group have routinely performed this synthetic sequence on a 100-gram scale. As not all macroline/sarpagine/ajmaline alkaloids are N1-substituted,



the tetracyclic ketone **32** has also been prepared[14] from **25** with a free N1-H. The synthesis was complicated by unwanted lactam formation, as shown in Scheme 8.



Scheme 8.

Acid/methanol-induced transformation of **27** to **29** did not occur, probably because the lactam moiety would destabilise the α-aryl cation intermediate. The reaction occurred as desired in the absence of a free carboxyl group, using **28** to give **29**. Upon exposure to base, **29** initially formed lactam **26**, but eventually gave the desired Dieckmann product **31** *via* **30**. Decarboxylation as before gave **32** (Scheme 9).

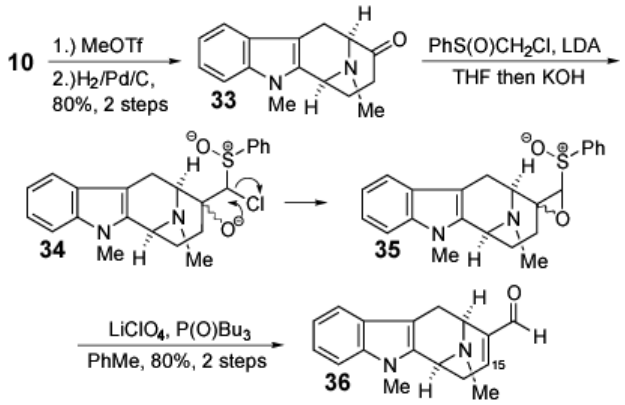
Scheme 9.

2.2. α,β-Unsaturated aldehyde formation and Claisen rearrangement: alstonerine, anhydromacrosalhine-methine and macrocarpamine

The tetracyclic ketone **10** was elaborated by Cook's group in the first total synthesis of (–)-alstonerine,[15] as shown in Scheme 10. Exchange of the N4-benzyl group for methyl to give **33** and elaboration of the ketone gave α,β-unsaturated aldehyde[16] **36** (*via* **34** and the intermediate epoxide **35**).

Scheme 10.

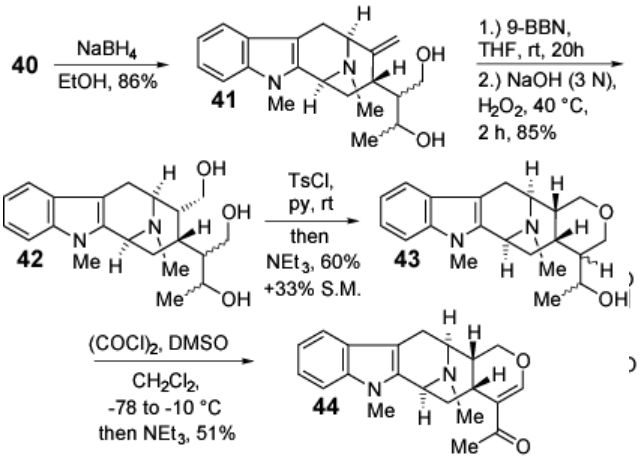
Studies had shown that intermolecular addition to the C15 position of **36** was not a facile process, so an intramolecular



strategy was used. Reduction of **36** to **37** and formation of vinylogous ester **39** using **38** allowed C15 functionalisation *via* a Claisen rearrangement to give **40** (Scheme 11).

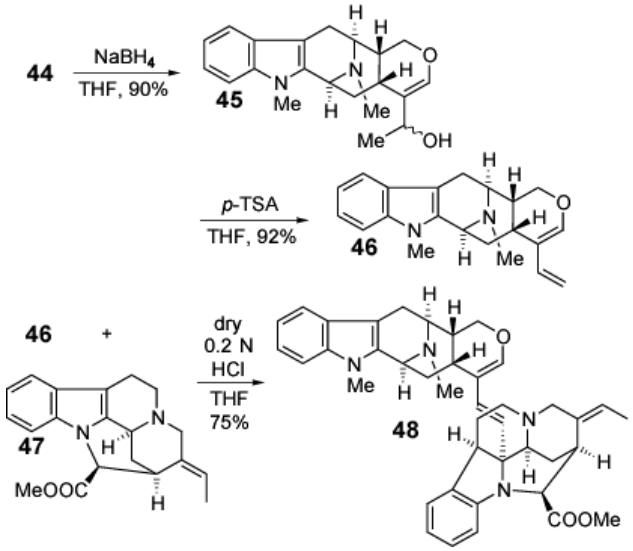
Scheme 11.

Carbonyl reduction and hydroboration gave triol **42** *via* **41**, and then selective tosylation of a primary alcohol and cyclisation gave **43**. A modified Swern oxidation[17] regenerated the vinylogous ester functionality and so led to (–)-alstonerine **44** (along with 31% dihydroalstonerine) in 8% overall yield from tetracyclic ketone **10** (not considering recycling of material) or 4% overall yield from D-tryptophan (Scheme 12).



Scheme 12.

The strategy detailed above for the synthesis of (–)-alstonerine **44** was later extended by Cook *et al.* for the synthesis[18,19] of (–)-anhydromacrosalhine methine **46**. Whilst not a natural product, this indole base constitutes the indole unit of the macroline-related bis(indole) alkaloid (–)-macrocarpamine **48**. Reduction of (–)-alstonerine **44** gave secondary alcohol **45**, which underwent acid-induced elimination to give (–)-anhydromacrosalhine methine **46**. Coupling of **46** with a natural sample of pleiocarpamine **47** (Scheme 13) completed the partial synthesis of (–)-macrocarpamine **48** (2% overall yield from D-tryptophan).

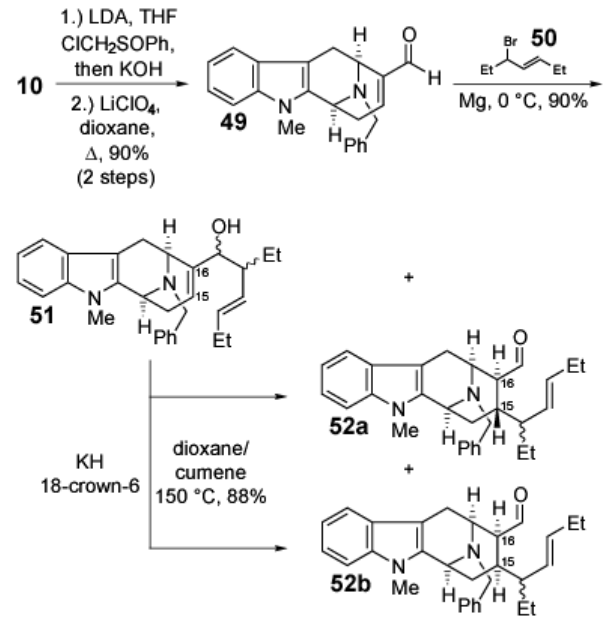


Scheme 13.

2.3. Ajmaline and alkaloid G

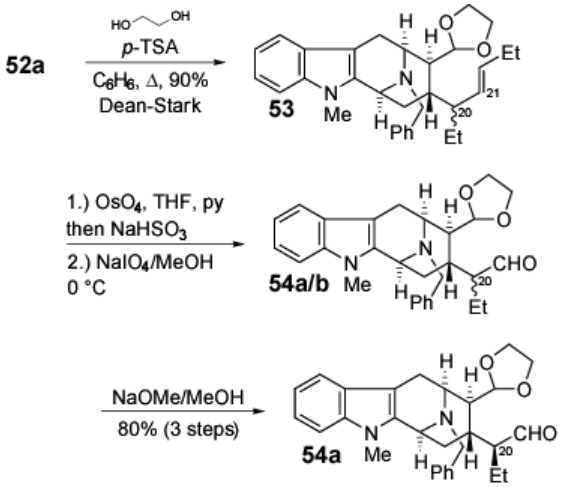
2.3.1. First-generation syntheses: 1,4-addition, oxyanion-Cope rearrangement and selective oxidations

Cook and co-workers employed the tetracyclic ketone **10** in the first total synthesis of (–)-ajmaline.[20,21] Ketone **10** was elaborated into α,β-unsaturated aldehyde **49** as before, although the reaction was found to proceed in the absence of the phosphine oxide (also the N4-benzyl group was still in place). As mentioned in Section 2.2, intramolecular C15 functionalisation had been found to be difficult, but it transpired that successful organometallic addition was possible by use of a Barbier–Grignard process. A *pseudo*-symmetric allyl bromide **50** was used to circumvent ambiguity regarding α- versus γ- addition. A mixture of 1,2- and 1,4-addition products resulted, as shown, but, in an elegant resolution to this problem, Cook was able to transform the undesired 1,2-addition product **51** into the 1,4-addition product **52** by means of an oxyanion-Cope rearrangement (Scheme 14).



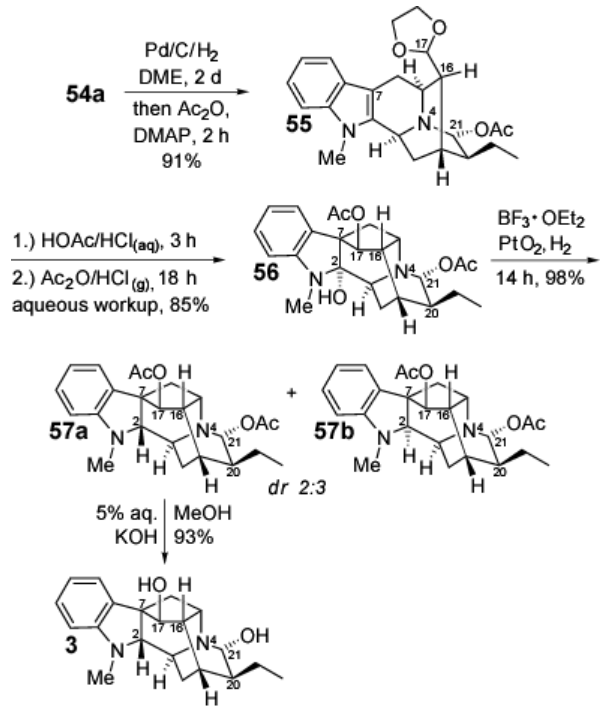
Scheme 14.

From the initial Barbier–Grignard reaction, **51** and **52** were formed in a ratio of 51:49. Of this, the 1,4-addition product **52** was formed in a ratio of **52a**:**52b** of 3:1, where **52a** was the desired isomer having the (15*S*) configuration. When **51** underwent an oxyanion-Cope rearrangement, **52a** and **52b** were isolated in a ratio of 3:2. Subsequent elaboration of **52a** was by ethylidene acetal protection of the aldehyde (giving **53**) and oxidative cleavage of the olefin. In order to effect chemoselective cleavage in the presence of the oxidatively-sensitive indole, a stoichiometric osmylation was required, with subsequent periodate cleavage of the resultant diol. At this point in the sequence it was possible to epimerise C20 *via* the aldehyde enolate, giving a **54a**:**54b** 1:1 epimeric mixture, separable by chromatography. With recycling of the undesired epimer **54b**, >80% conversion from **53** was possible (Scheme 15).



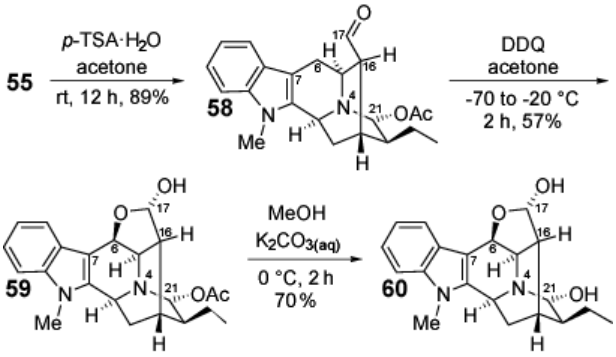
Scheme 15.

N4-deprotection allowed formation of the *O*-acetyl aminal **55**. Treatment with $HCl_{(aq)}$/AcOH, then $Ac_2O/HCl_{(g)}$, effected the final cyclisation to the ajmalan skeleton by electrophilic addition to C7. The resultant C2 hemiaminal **56** was reduced under Lewis acidic conditions to furnish a C2-epimeric mixture, **57a**:**57b** of 2:3. The epimer having the correct C2 configuration, **57a**, underwent base-mediated hydrolysis to afford (–)-ajmaline **3** (Scheme 16) in 11% yield from tetracyclic ketone **10** (5% from D-tryptophan). Whilst the formation of only 40% of the desired C2 epimer in the penultimate step is not ideal, Cook notes that 2-*epi*-diacetyl ajmaline **57b** is the thermodynamic product and many reagent systems provide solely **57b**.



Scheme 16.

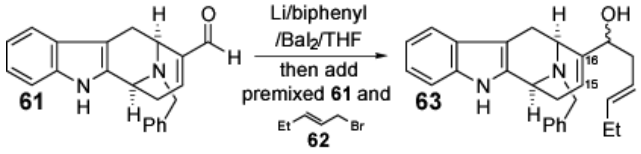
Hydrolysis of acetal **55** gave **58**, which had previously been converted *via* **59** into alkaloid G by Stöckigt and co-workers[22] (Scheme 17), employing a DDQ oxidation to functionalise the C6 position. Cook's report therefore constitutes a formal synthesis of alkaloid G **60** in 10 steps and 12% yield from tetracyclic ketone **10** (6% overall yield from D-tryptophan).



Scheme 17.

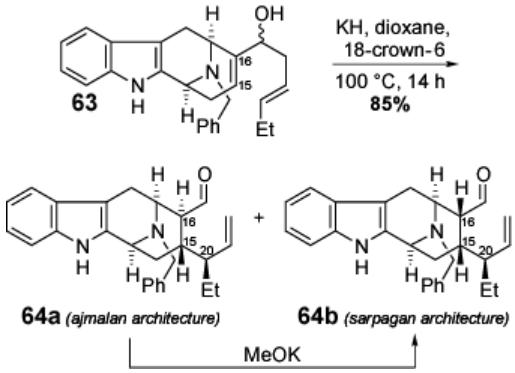
2.3.2. Second-generation syntheses: organobarium chemistry and kinetic enolate quenching

Shortly after the reports summarised in Section 2.3.1, Cook's group published improved syntheses of (–)-ajmaline[23] and alkaloid G.[23,24] The improvements address the issue of stereocontrol in the organometallic addition and oxyanion-Cope steps. Using methodology due to Yamamoto,[25] Cook and co-workers treated N1-unsubstituted α,β-unsaturated aldehyde **61** with an organobarium reagent derived from (*E*)-pent-2-enyl bromide **62**. This addition took place solely from the α-position of the metallate, hence the need for a *pseudo*-symmetric alkenyl halide was removed. Additionally, only 1,2-addition to **61** was observed, giving **63** as the sole product (Scheme 18).



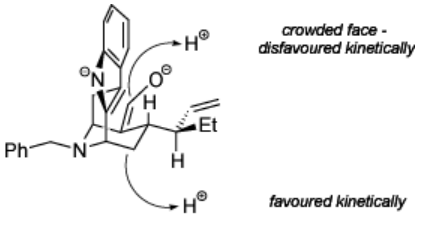
Scheme 18.

Oxyanion-Cope rearrangement of **63** took place as before; in this instance, however, near total selectivity for the desired configurations was observed at C15 *and* C20 (*c.f.* selectivity of 3:2 in Section 2.3.1). At C16, in the first instance, the selectivity was 1:4 for **64a**:**64b** for the undesired sarpagan (16*R*) configuration. Upon prolonged exposure of (16*S*) **64a** to base, epimerisation to mostly (16*R*) **64b** was observed, implying **64b** was the thermodynamic product (Scheme 19).



Scheme 19.

The 3D structure (Scheme 20) of the enolate resulting from the oxyanion-Cope rearrangement suggested that the α-face might be less hindered and as such **64a** might be the kinetic product. After optimisation, it was found that quenching the oxyanion-Cope rearrangement with 1 N trifluoroacetic acid at low temperature favoured the formation of **64a**. After the rearrangement had gone to completion, THF was added, allowing the reaction mixture to be cooled below the melting point of dioxane. At –100 °C in dioxane:THF, addition of 1 N trifluoroacetic acid in THF afforded **64a**:**64b** in a ratio of 43:1.



Scheme 20.

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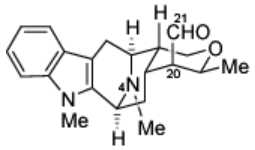
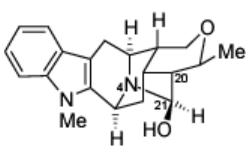


(–)-talcarpine **65**



(–)-talpinine **66**

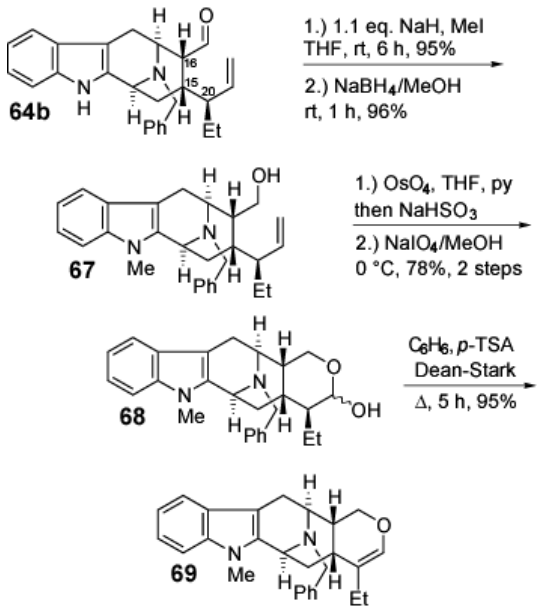
to vary reaction conditions to favour either **64a** or **64b** permits stereospecific entry to either the macroline/sarpagine (16*R*) series or the ajmaline (16*S*) series. Aldehyde **64a** was protected as the ethylidene acetal and then N1-methylated to converge on the (–)-ajmaline synthesis detailed in Section 2.3.1. The second-generation synthesis was thus completed in 9% overall yield from D-tryptophan methyl ester, an appreciable improvement. In completing the second-generation synthesis of alkaloid G, Cook's laboratory reports a significant improvement to the DDQ-mediated α-aryl oxidation step – performing the reaction in wet THF leads to a yield of 94% of **42** (one diastereoisomer only). The improved alkaloid G synthesis was therefore completed in 25% overall yield from D-tryptophan methyl ester.

2.4. Selenium chemistry and an unusual pyrolytic rearrangement: talpinine, talcarpine, alstonerine and anhydromacrosalhine-methine

Cook *et al.* have reported syntheses[26,27] of the two structurally related macroline/sarpagine alkaloids, (–)-talcarpine **65** and (–)-talpinine **66**. They employ much of the methodology used for the synthesis of (–)-ajmaline and alkaloid G. It may be seen (Scheme 21) that **65** and **66** are epimeric at C20 and that **66** lacks the N4-methyl group, but has a hemiaminal moiety containing a C21-N4 linkage.

Scheme 21.

The synthetic sequence was executed as per Section 2.3.2, this time from the N1-unsubstituted tetracyclic ketone **32**. As the sarpagan configuration (16*R*) was required in this instance, the enolate deriving from the oxyanion-Cope rearrangement was quenched under thermodynamic conditions, simply by adding MeOH to the reaction mixture and stirring at room temperature for 2 h to give **64b**. After N1-methylation, the aldehyde moiety was reduced and oxidative olefin cleavage (as previously) this time afforded a diastereoisomeric mixture of lactols **68**, which were then dehydrated (Scheme 22).

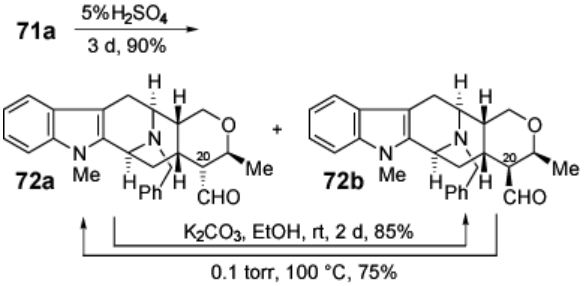


Scheme 22.

A key feature of this synthesis is the use of *N*-(pehnylseleno)phthalimide to effect the addition of selenium[28] and a methoxy group across the enol ether, giving **709**, followed by selenium oxidation and elimination with rearrangement to afford a mixture of exocyclic olefin geometries (Scheme 23) in a ratio **71a**:**71b** of 4:1 (where **71a** is the desired isomer).

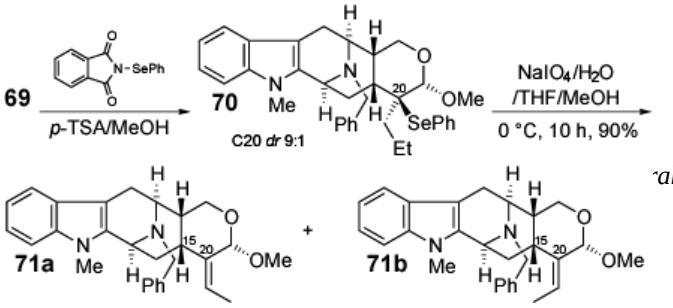
Scheme 23.

The desired isomer **71a** was treated with 5% H_2SO_4 for 3 days, which induced acetal opening, C15-C20 bond rotation and Michael addition, to generate saturated C20-aldehydes as a C20 epimeric mixture, 3:5 of **72a**:**72b**. Aldehyde **72a** (20*R* configuration) is the precursor of talpinine and, similarly, **72b** (20*S* configuration) is the precursor of talcarpine. The two epimeric precursors may, in fact, be interconverted (Scheme 24).



Scheme 24.

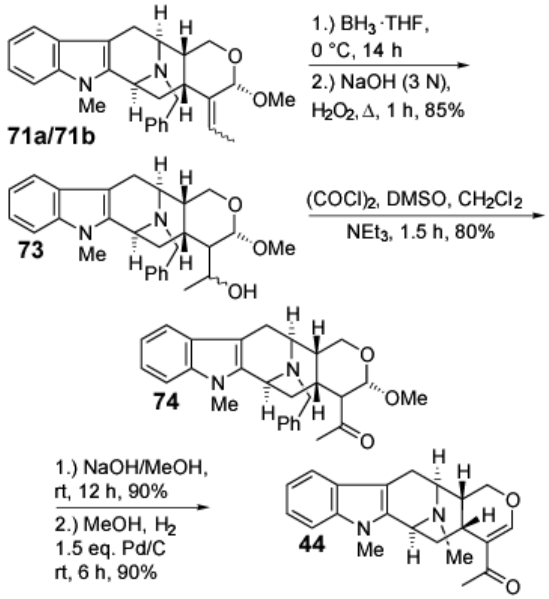
Conversion of **72a** into **72b** is simply base-induced epimerisation to the thermodynamic product. The pyrolytic conversion[29] of **72b** into **72a** is not fully understood mechanistically. Conversion of **72a** into talpinine (10% from D-tryptophan, Scheme 25) was effected simply by N4-debenzylation (with spontaneous hemiaminal formation). Conversion of **72b** into talcarpine (10% from D-tryptophan, Scheme 25) was effected by N4-debenzylation with concomitant N4-methylation, a transformation speculated to involve *in-situ* formaldehyde formation.



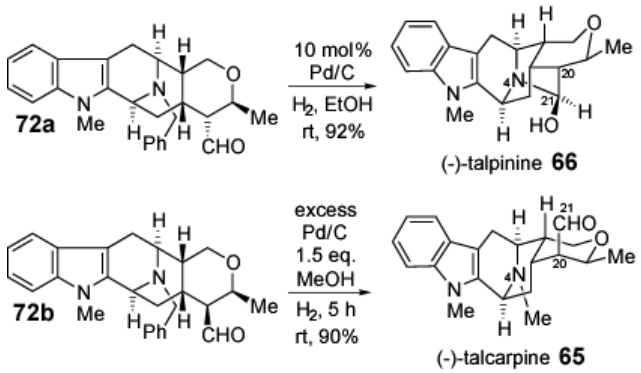
Scheme 25.

The methodology detailed above has also been employed in the second-generation syntheses[27] of anhydromacrosalhine-methine and alstonerine. The geometric mixture of olefins (**71a** and **71b**) was subjected to hydroboration, Swern oxidation, elimination of methanol and N4-debenzylation/methylation to furnish (–)-alstonerine **44** (Scheme 26) *via* **73** and **74** in an improved 12% overall yield from D-tryptophan (*c.f.* Section 2.2).

Scheme 26.



Anhydromacrosalhine-methine **46** was synthesised from **69** (Scheme 27), by N4-debenzylation/methylation at an earlier stage, then selenium introduction, oxidation and

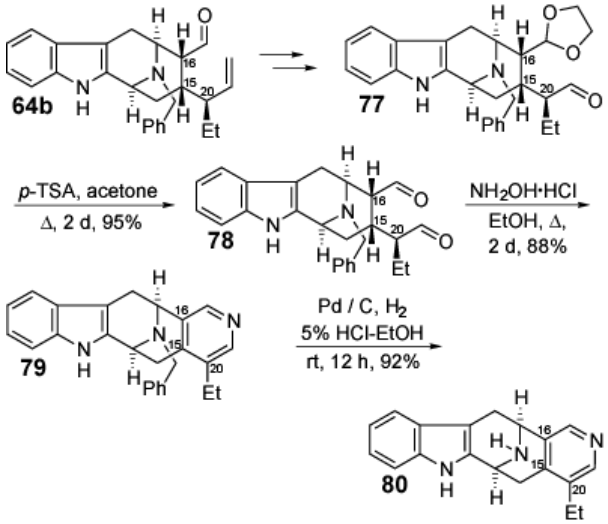


elimination as before, followed by acid-induced elimination to the vinylogous enol ether product **46** *via* **75** and **76** (14% from D-tryptophan, *c.f.* Section 2.2).

Scheme 27.

2.5. Pyridine formation: norsuaveoline

Cook's laboratory has also reported the synthesis of the pyridyl macroline alkaloid, norsuaveoline.[21,30] This synthesis has much in common with Cook's earlier synthesis of suaveoline.[31] From the N1-unsubstituted tetracyclic ketone **32**, the synthesis proceeded as per the ajmaline synthesis in Section 2.3.2. Cook and co-workers opted to use the sarpagan C16-configured oxyanion-Cope product, although, in this instance, the configurations of C15, C16 and C20 are of less concern, since all are ultimately incorporated into the pyridine ring. Ethylidene acetal formation and oxidative olefin cleavage were executed as before to give **77**. In this case, however, the acetal was deprotected to furnish a 1,5-dialdehyde **78**. This was treated with ethanolic hydroxylamine hydrochloride to access the pyridine ring directly; N4-debenzylation of **79** afforded norsuaveoline **80** in 28% yield from D-tryptophan methyl ester (Scheme 28).

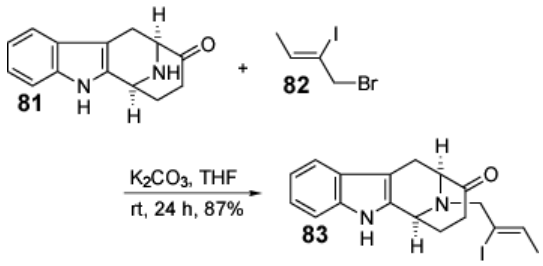


Scheme 28.

2.6. Palladium sarpagan methodology: *ent*-affinisine, 16-*epi*-affinisine, alkaloid Q3, dehydro-16-*epi*-affinisine, koumidine, 16-*epi*-*N*-methylpericyclivine, *N*-methylvellosimine, normacusine B, 16-*epi*-normacusine B, panarine and vellosimine

For the synthesis of alkaloids possessing the sarpagan skeleton, a key question is how to construct the skeleton such that the C19-C20 olefin geometry is controlled. Cook attempted to address this problem in various ways and met

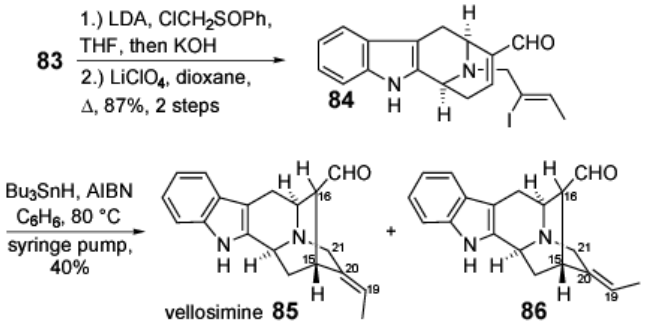
with success when he employed a palladium-mediated cyclisation. The key reaction may be illustrated with the example of Cook's total synthesis[32,33] of (+)-vellosimine **85**. The iodoalkene **82** (which has been employed by other workers[34-40]) was reacted with the N1-unsubstituted, N4-



debenzylated tetracyclic ketone **81** to give **83** (Scheme 29).

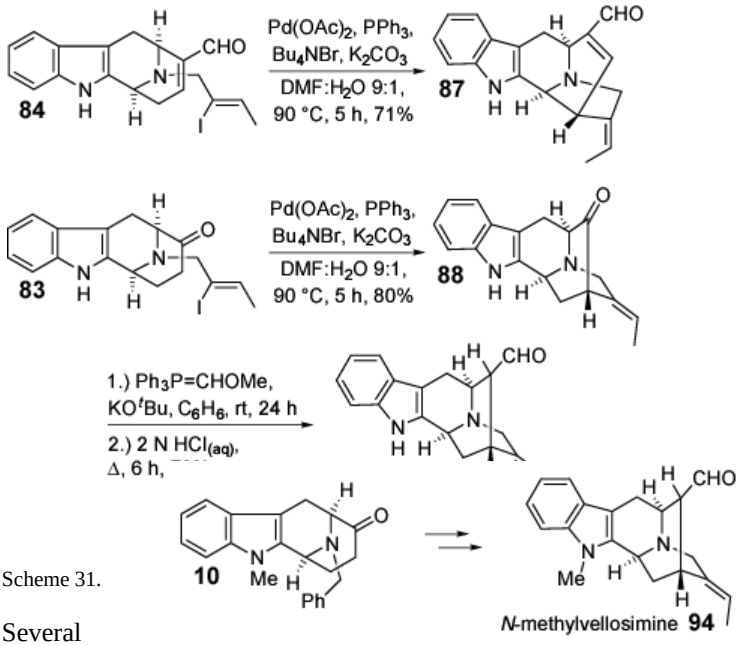
Scheme 29.

Ketone **83** was elaborated to the corresponding α,β-unsaturated aldehyde **84,** as previously. One can envisage that transmetallation and Michael addition would give access to the sarpagan skeleton, but, in fact, this approach was unsuccessful. Instead, it was found that a radical-mediated coupling could effect C15-C20 bond formation. This occurred with scrambling of the C19-C20 olefin geometry, however, and the desired (+)-vellosimine **85** was the minor product in a ratio **85**:**86** of 1:3 (Scheme 30).



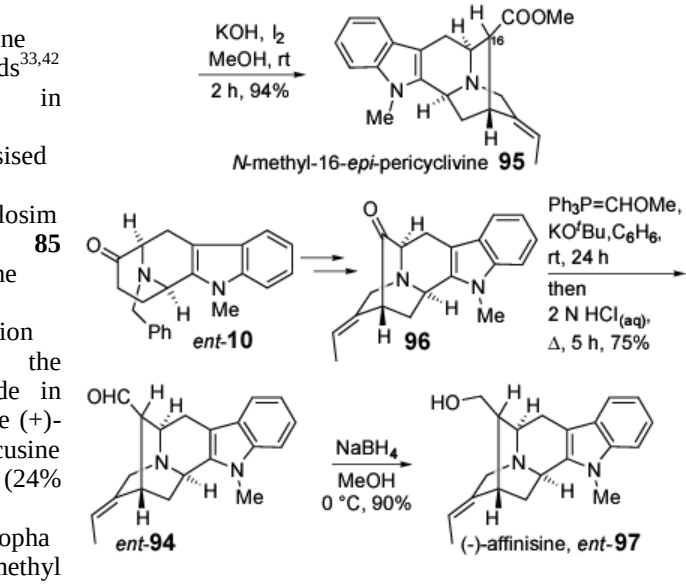
Scheme 30.

In view of the failure of both metallate and radical methods, the desired stereospecific cyclisation of **84** was attempted under Pd^0 catalysis. The unexpected product **87** was isolated (as a single geometric isomer), presumably arising from the enolate of **84**. Such a cyclisation had been previously observed in other systems.[41] By inference from this result, it followed that **83** might undergo cyclisation to the desired vellosimine skeleton. Ketone **83** did, indeed, give **88** stereospecifically under the same conditions. This was transformed into (+)-vellosimine **85** *via* a masked aldehyde, which was unmasked and epimerised to the more stable C16 sarpagan configuration (Scheme 31). The first total synthesis of this sarpagine alkaloid was therefore completed in 27% overall yield from D-tryptophan methyl ester.



Scheme 31.

Several more sarpagine alkaloids[33,42] were, in turn, synthesised from (+)-vellosimine **85** (Scheme 32). Reduction of the aldehyde in **85** gave (+)-normacusine B **89** (24% from D-tryptophan methyl ester). Conversely, oxidation of the aldehyde in **85** and esterification gave **90**, quaternisation of which with methyl iodide (to furnish **91**) and subsequent anion exchange gave (–)-alkaloid Q3 **92** (18% from D-tryptophan methyl ester). Ester hydrolysis of **92** and neutralisation gave zwitterionic (–)-panarine **93** (16% from D-tryptophan methyl ester).



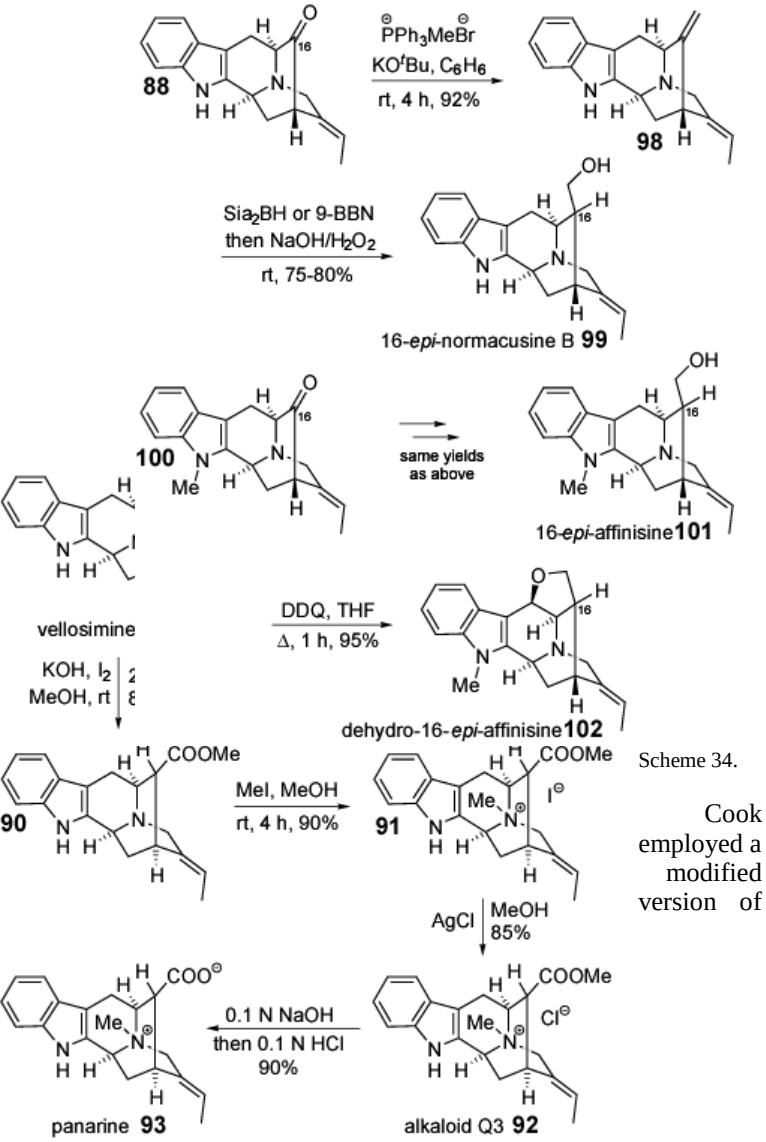
Scheme 32.

The same synthetic sequence used to prepare (+)-vellosimine was applied to the N1-methyl tetracyclic ketone **10** to produce (+)-*N*-methylvellosimine[33] **94** (29% overall yield from D-tryptophan, Scheme 33). Oxidation and esterification provided (+)-*N*-methyl-16-*epi*-pericyclivine[33] **95** (27% overall yield from D-tryptophan). Reduction of the aldehyde in **94** provided (+)-affinisine[33]

97 (26% overall yield from D-tryptophan). Cook's group also executed the entire synthetic sequence from L-tryptophan, *via* **96**, thus providing *ent*-**97** (–)-affinisine,[43] the enantiomer of the natural product (Scheme 33). This *ent*-affinisine was required for the synthesis of "mismatched" unnatural bis(indole) alkaloids, to probe their biological activities and SAR. As LeQuesne had previously reported[44,45] partial syntheses of macroline **1** and alstonerine **44** from affinisine, Cook's work constitutes formal syntheses of the antipodes of these alkaloids also.

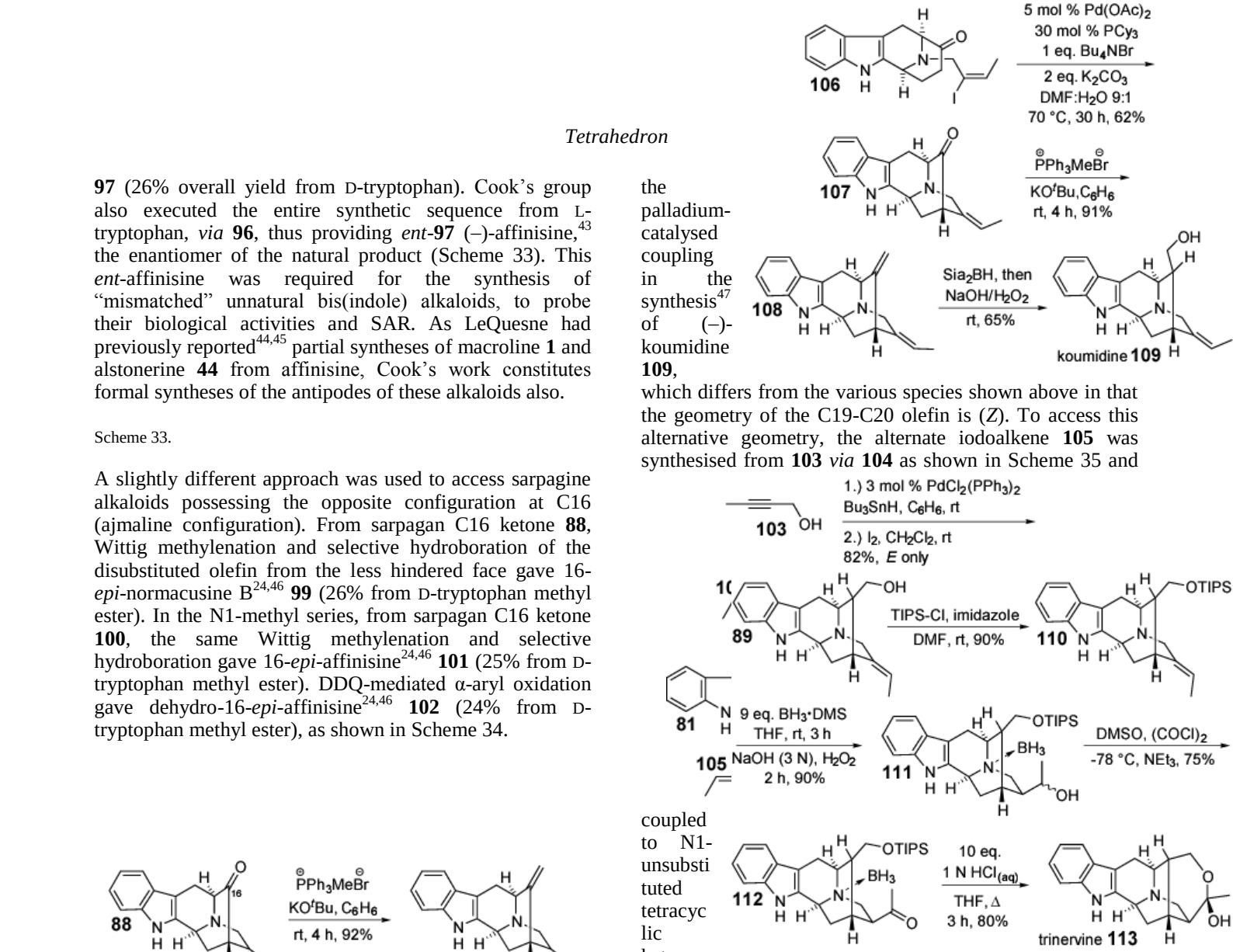
Scheme 33.

A slightly different approach was used to access sarpagine alkaloids possessing the opposite configuration at C16 (ajmaline configuration). From sarpagan C16 ketone **88**, Wittig methylenation and selective hydroboration of the disubstituted olefin from the less hindered face gave 16-*epi*-normacusine B[24,46] **99** (26% from D-tryptophan methyl ester). In the N1-methyl series, from sarpagan C16 ketone **100**, the same Wittig methylenation and selective hydroboration gave 16-*epi*-affinisine[24,46] **101** (25% from D-tryptophan methyl ester). DDQ-mediated α-aryl oxidation gave dehydro-16-*epi*-affinisine[24,46] **102** (24% from D-tryptophan methyl ester), as shown in Scheme 34.



Scheme 34.

Cook employed a modified version of the palladium-catalysed coupling in the synthesis[47] of (–)-koumidine **109**, which differs from the various species shown above in that the geometry of the C19-C20 olefin is (*Z*). To access this alternative geometry, the alternate iodoalkene **105** was synthesised from **103** *via* **104** as shown in Scheme 35 and coupled to N1-unsubstituted tetracyclic ketone **81**.



Scheme 35.

The palladium-mediated cyclisation was less facile than in previous examples with the opposite (*E*) olefin geometry – despite much optimisation, on reaction of **106** significant amounts of dealkylated product **81** were isolated along with the desired **107**. Completion of the synthesis (Scheme 36) was *via* hydroboration of **108** as for the other C-16-*epi* alkaloids, in 21% yield from D-tryptophan methyl ester.

Scheme 36.

2.7. Selective hydroboration: trinervine

The sarpagine alkaloid trinervine **113**, a cyclic hemiacetal, was synthesised from (+)-normacusine B **89**, the synthesis of which is detailed in Section 2.6. Silylation of the alcohol was followed by attempts at selective hydroboration of the trisubstituted C19-C20 olefin (Scheme 37). Surprisingly, the initial selectivity (at 0 °C) for the secondary hydroxyl product **111** over the tertiary regioisomer was only 7:3. It was postulated that this may be due to complexation of the first equivalent of borane to N4, thus altering the electronic characteristics of the olefin. A detailed optimisation study

was carried out[48] – use of bulky hydroborating agents resulted in no reaction, but increased selectivity was observed by using **110** (with R = TIPS) at room temperature, furnishing the desired regioisomer in a ratio of 25:1. This was oxidised, in turn, to the ketone and upon deprotection of the hydroxyl group in **112** (and cleavage of the borane adduct), spontaneous cyclisation gave trinervine **113** (20% from tetracyclic ketone **32**).

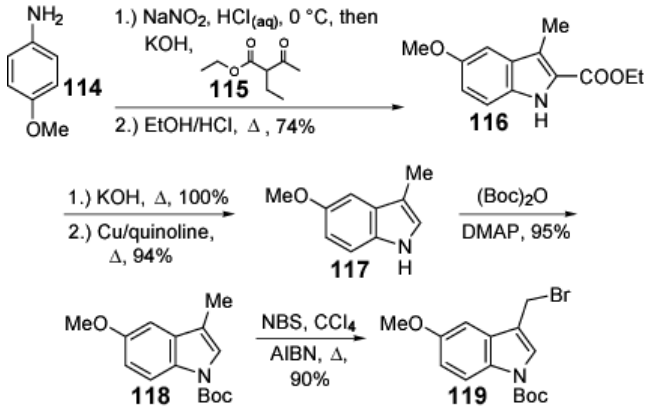
Scheme 37.

2.8. Indole oxygenation

As alluded to in the introduction, many macroline/sarpagine/ajmaline alkaloids possess indole ring oxygenation. Cook has synthesised many of these and the key to these syntheses has been the optimisation of routes to the relevant oxygenated tryptophan derivatives. Cook has successfully introduced oxygenation in the C10-, C11- and C12-positions. In each instance, the Schöllkopf chiral auxiliary[49] was used to introduce the correct amino acid stereochemistry. The precise details vary depending on the ring substitution pattern, however, and so will be discussed individually.

2.8.1. C10 oxygenation: majvinine, 10-methoxyaffinisine, *N*-methylsarpagine and macralstonidine

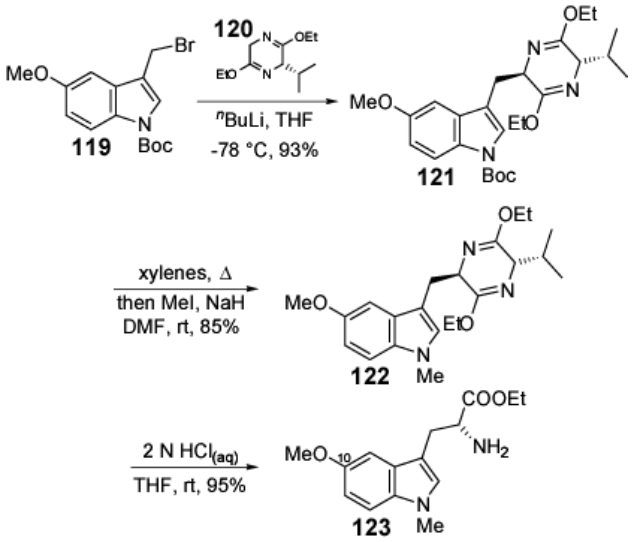
p-Anisidine was employed as a starting material for a synthesis[50,51] that Cook's laboratory has executed on a > 600-gram scale (Scheme 38). Fischer indole formation *via* a Japp–Klingemann azo-ester intermediate[52,53] formed from **114** and **115** gave the trisubstituted indole **116**. C2-Decarboxylation to give **117** was followed by N1-protection, either with a Boc group (giving **118**) or as a sulfonamide (only the Boc series is considered here). Optimisation of the brominating conditions[51] was required to access the desired α-aryl brominated product **119** and



avoid indolyl C2-bromination.

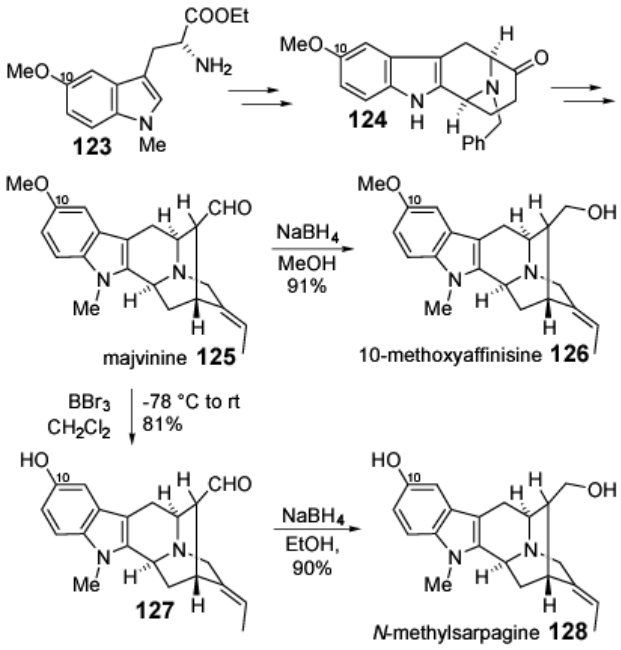
Scheme 38.

Cook has studied the effect of the leaving group and other parameters on the diastereoselectivity of the reaction with Schöllkopf auxiliaries.[54,55] Bromide **119** was coupled with the Schöllkopf auxiliary **120** (derived from L-valine) to give **121** as a single diastereoisomer. The Boc group was cleaved thermolytically, followed by N1-methylation in one pot, giving **122**. The auxiliary was removed under conditions of acidic hydrolysis to furnish **123**, the C10-methoxy analogue of D-tryptophan ethyl ester (Scheme 39).



Scheme 39.

The ring-oxygenated amino acid **123** was amenable to the chemistry developed by Cook and co-workers detailed in Sections 2.1 to 2.7. Thus, the synthesis of C10-methoxy tetracyclic ketone **124** was high yielding (although it was necessary to avoid harshly acidic conditions in the Pictet–Spengler and C3-isomerisation steps, otherwise decomposition of the indole occurred). The conversion of **124** to the sarpagan skeleton *via* the palladium enolate methodology described previously was similarly high yielding (Scheme 40). Synthesis of (+)-majvinine **125** (28% yield from C10-methoxy D-tryptophan ethyl ester analogue **123**) was executed as per *N*-methylvellosimine **94**

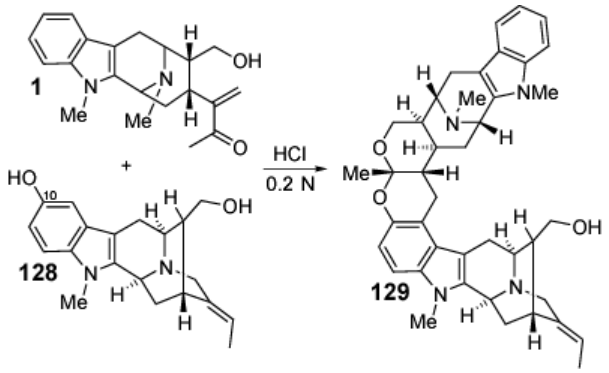


(majvinine is simply the C10-methoxy analogue of **94**). Reduction of the aldehyde moiety in **125** gave

Scheme 40.

(+)-10-methoxyaffinisine **126** (25% yield from **123**). For the synthesis of (+)-*N*-methylsarpagine **128**, a C10-hydroxy group was required as opposed to a C10-methoxy group. Therefore, (+)-majvinine **125** was demethylated with boron tribromide (giving **127**) prior to reduction to (+)-*N*-methylsarpagine **128** (20% yield from **123**).

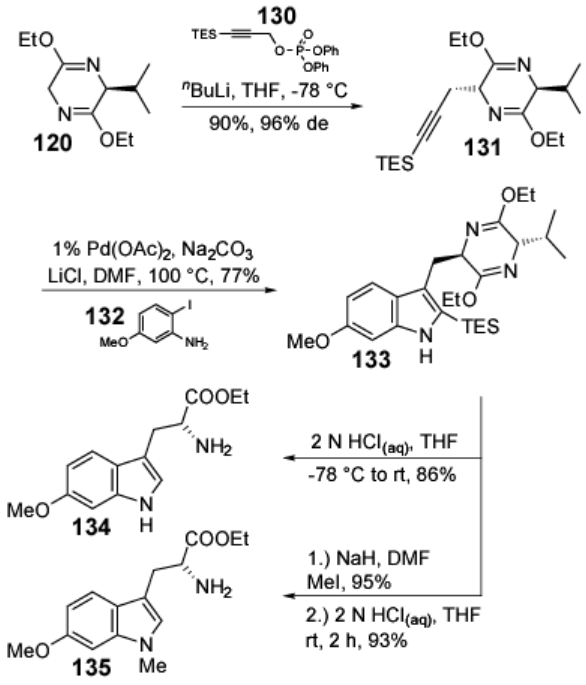
Cook also reported the first total synthesis of the bis(indole) alkaloid, (+)-macralstonidine **129**, from the coupling[45] of synthetic *N*-methylsarpagine **128** with synthetic macroline **1** (Scheme 41).



Scheme 41.

2.8.2. C11 oxygenation: gardnerine, gardnutine, 11-methoxyaffinisine and 16-*epi*-*N*-methylgardneral

Synthesis of a C11-oxygenated tryptophan analogue would have been subject to regiochemical ambiguity if attempted *via* a Fischer indole formation. Cook and co-workers

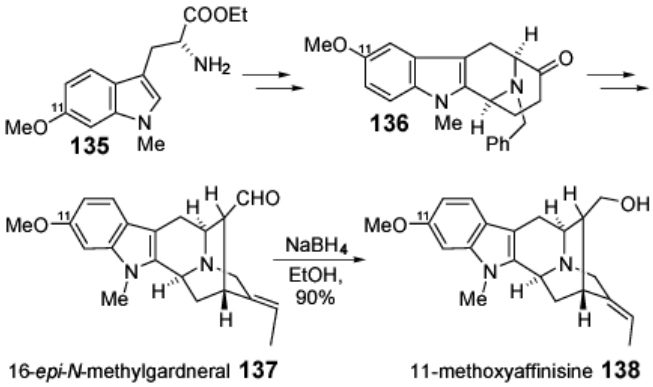


accessed this series[56] by means of a Larock hetero-

Scheme 42.

annulation.[57] The order of events is reversed from that in Section 2.8.1, in that reaction of **130** with the Schöllkopf auxiliary occurs prior to indole formation with **132** to give **133** (Scheme 42). The formation of **131** in high *de* is due in part to the choice of phosphonate leaving group.[54] The Larock heteroannulation has been carried out on a 300-gram scale.

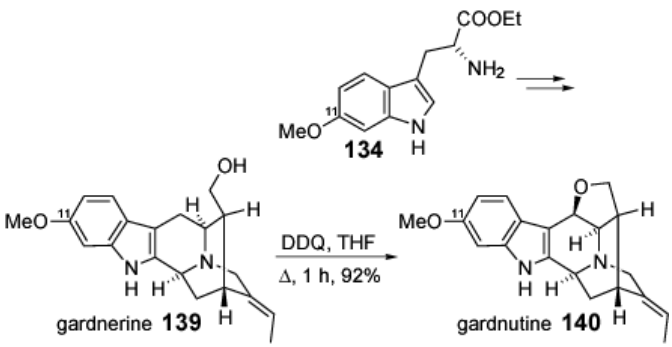
Both N1-methyl and N1-unsubstituted amino acids are easily accessible by this method. Once again, Cook's previously developed methodology was *via*ble with these C11-oxygenated amino acids (Scheme 43): (+)-16-*epi*-*N*-methylgardneral **137** was synthesised *via* **136** (35% from C11-methoxy, N1-methyl D-tryptophan ethyl ester **135**) as per *N*-methylvellosimine **94** (Section 2.6, **137** is simply the C11-methoxy analogue of **94**). Reduction of **137** gave 11-methoxyaffinisine **138** (32% from **91**). Note that **137** and **138** have not been isolated from a natural source to date; they are precursors of natural products discussed in



Sections 2.11 and 2.12.

Scheme 43.

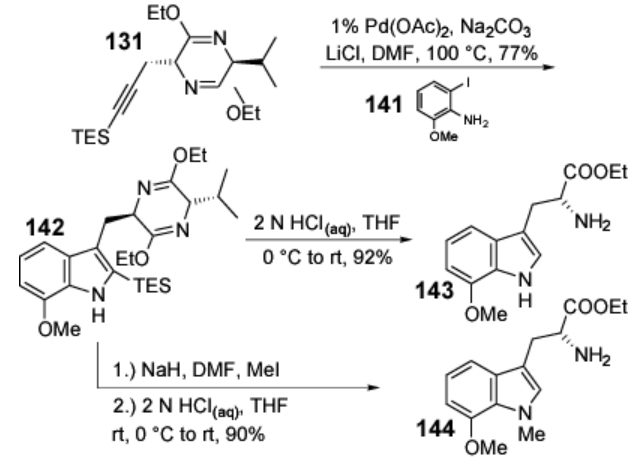
(–)-Gardnerine **139** and (+)-gardnutine **140** are N1-unsubstituted C11-methoxy sarpagine alkaloids synthesised from C11-methoxy D-tryptophan ethyl ester **134** by Cook and co-workers[58] in a manner analogous to that for 16-*epi*-normacusine B **99** (Section 2.6, **139** is simply the 11-methoxy analogue of **99**). (–)-Gardnerine **139** was synthesised in 20% overall yield from **134**. (+)-Gardnutine **140** was synthesised from **139** by DDQ-mediated α-aryl oxidation (18% overall yield from **134**, Scheme 44).



Scheme 44.

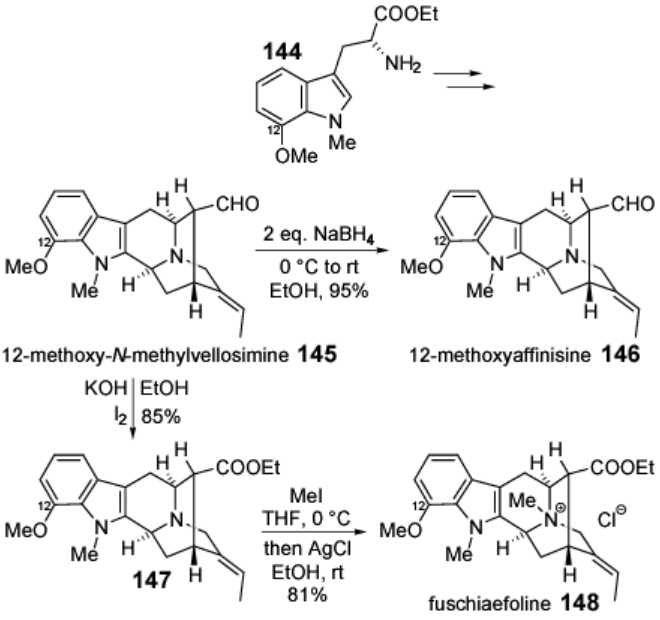
2.8.3. C12 oxygenation: fuchsiaefoline, 12-methoxyaffinisine and 12-methoxy-*N*-methylvellosimine

The required C12-methoxy amino acids were prepared by the same process used for the C11-methoxy series (namely a Larock heteroannulation), employing a regioisomeric iodoanisidine **141**, giving **142** as a common intermediate for the synthesis of **143** and **144** (Scheme 45).



Scheme 45.

The C12-methoxy amino acids were compatible with Cook's previously developed methodology, thus permitting the synthesis[59,60] of (+)-12-methoxy-*N*-methylvellosimine **145** (overall yield 40% from **144**) and (+)-12-methoxyaffinisine **146** (overall yield 38% from **144**) as per the unsubstituted analogues **85** and **97**. The quaternary alkaloid (–)-fuschiaefoline **148** was synthesised *via* **147** (27% yield from **144**) in two steps from **145** (Scheme 46).



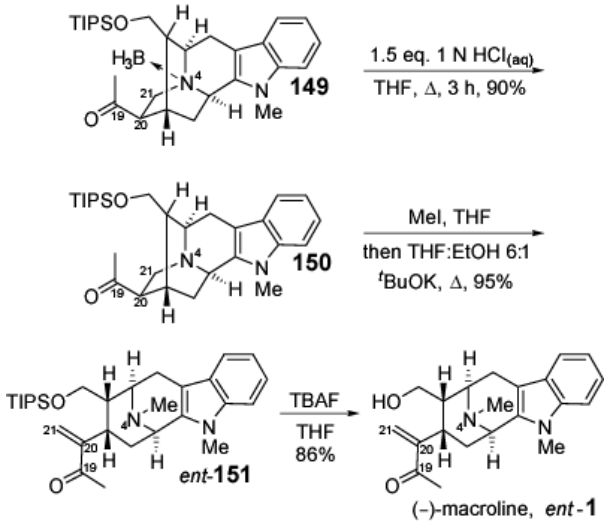
Scheme 46.

2.9. Hofmann elimination: alstophylline, *ent*-macroline, 11-methoxymacroline, macralstonine

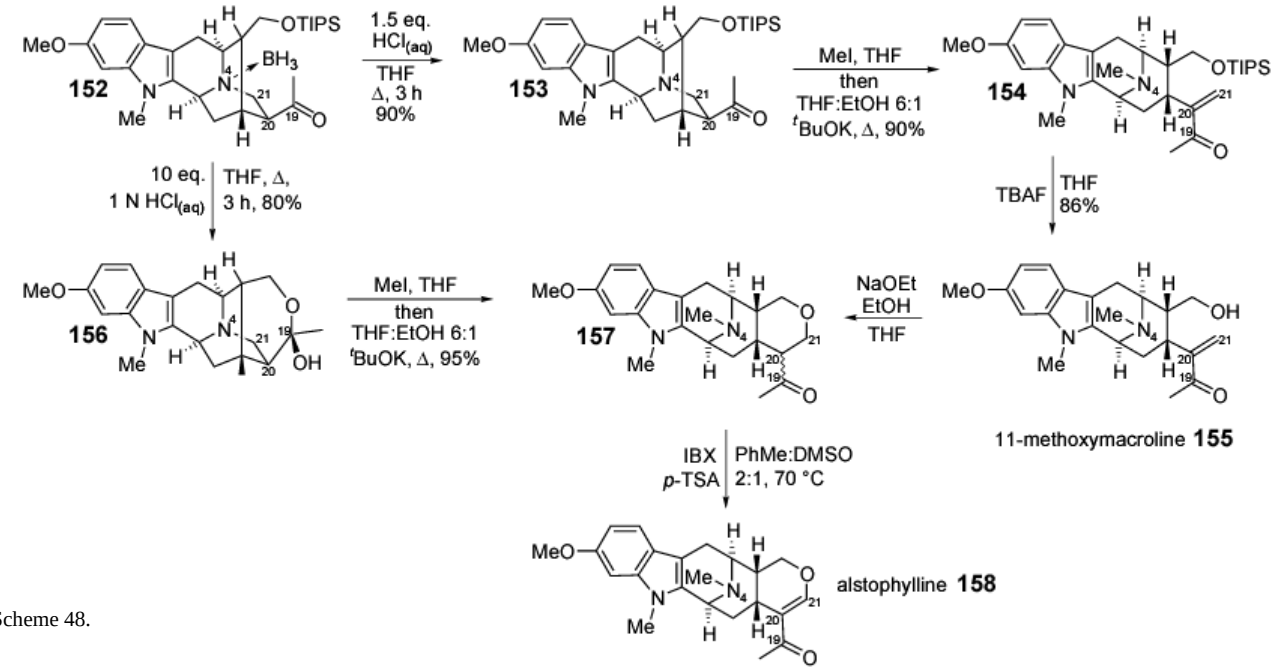
As mentioned in the introduction, the macroline skeleton may be accessed by Hofmann elimination of the sarpagine skeleton, a transformation used by Cook to synthesise many macroline alkaloids. For example,[61] starting from L-tryptophan, Cook *et al.* synthesised **149**, the enantiomer of the N1-methyl analogue of C19-oxo borane adduct **112** from the synthesis of trinervine (Section 2.7). Whereas in the trinervine synthesis **112** was treated with excess acid to effect both dative bond scission and desilylation, in this instance **149** was treated with a small excess of acid, removing the borane, but leaving the silyl group intact to give **150**. N4 was quaternised with methyl iodide, then under basic conditions Hofmann elimination occurred with regiospecific N4-C21 bond scission to give *O*-silylated macroline derivative *ent*-**151**. This was stable upon storage, or could be deprotected to give reactive (–)-macroline, *ent*-**1** (Scheme 47), in 12% overall yield from L-tryptophan methyl ester (intended for use in the synthesis of mismatched bis(indole) alkaloid analogues).

Scheme 47.

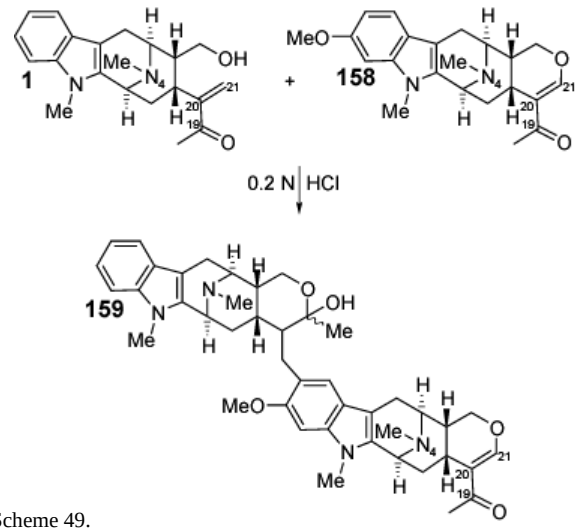
11-Methoxymacroline **155** was synthesised[56] by an entirely analogous route from the (naturally configured) 11-



methoxy amino acid ester **134** (detailed in Section 2.8.2) in 14% overall yield. (–)-Alstophylline **158** (the 11-methoxy analogue of alstonerine **44**) was also synthesised by this route[56] – in this case, two possible pathways were available, only one of which utilised 11-methoxymacroline **155** as an intermediate (*via* **152**, **153** and **154**, Scheme 48), the other being *via* **156**. The final step in the synthesis of (–)-alstophylline **158** is an IBX-mediated oxidation of common intermediate **157**. Note that the yields are not quoted for all steps (preliminary communication). The bis(indole) alkaloid, macralstonine **159**, was synthesised by the protocol of LeQuesne and Cook[62] from macroline and alstophylline monomer units (Scheme 49).

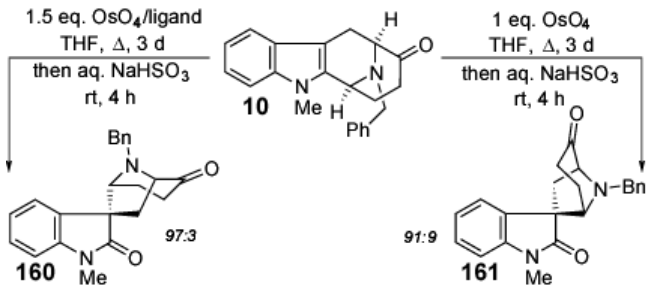


Scheme 48.



Scheme 49.

(–)-alstonerine **44**, detailed in Section 2.4) was oxidised diastereoselectively to furnish oxindole **162** as the sole diastereoisomer. Cook proposes that coordination of the N4 lone pair to the osmium enhances the selectivity. N4-Debenzylation was followed by elimination to form the vinylogous ester product (+)-alstonisine **163** (12% overall yield from D-tryptophan, Scheme 51).

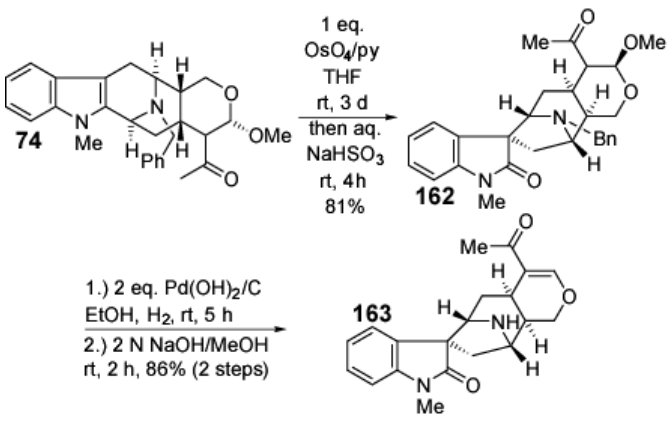


Scheme 50.

2.10. Diastereospecific oxindole formation: alstonisine

Brief consideration will be given to Cook's synthesis of the macroline-related oxindole (+)-alstonisine **163**. Oxindoles may be formed from the corresponding indoles by C2-C7 oxidation, with rearrangement to the C7-spirocyclic skeleton in the case of tetrahydro-β-carbolines. Model studies performed by Cook[63] on the tetracyclic ketone **10** (Scheme 50) led to the discovery that if osmium tetroxide were used as oxidant, a particular diastereoisomer (**160** or **161**) could be favoured by the presence or absence of a Sharpless ligand (quinuclidine, DHQ-CLB, DHQD-CLB, $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ were used).

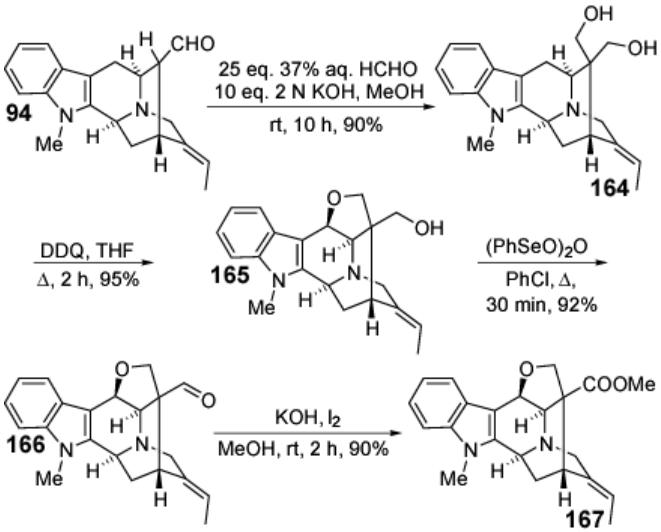
Cook applied the findings from the model studies to the synthesis[64] of (+)-alstonisine. Acetal **74** (a late-stage intermediate from the second-generation synthesis of



Scheme 51.

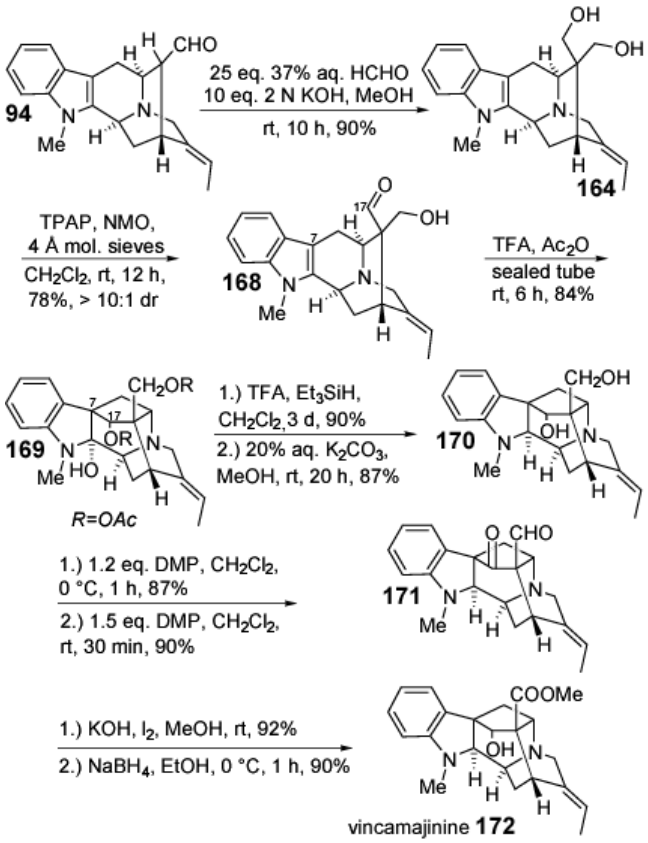
2.11. Tollens reaction: dehydrovoachalotine, 11-methoxy-17-*epi*-vincamajine and vincamajinine

Various sarpagine/ajmaline-related alkaloids are known which have a quaternary C16 motif. To access this substitution pattern from tertiary C16 species such as those dealt with in Sections 2.6-2.8, Cook *et al.* employed the Tollens reaction. For example, in the synthesis[65,66] of (+)-dehydrovoachalotine **167**, *N*-methylvellosimine **94** was transformed into the 1,3-diol **164** in a yield of up to 90% after optimisation (Scheme 52). DDQ-mediated α-aryl oxidation was high yielding, as before, but oxidation of the neopentyl hydroxyl group in **165** proved problematic; eventually, it was found that a selenium-mediated oxidation furnished the aldehyde **166**, which, in turn, could be oxidised to (+)-dehydrovoachalotine **167** (21% overall yield from D-tryptophan).



Scheme 52.

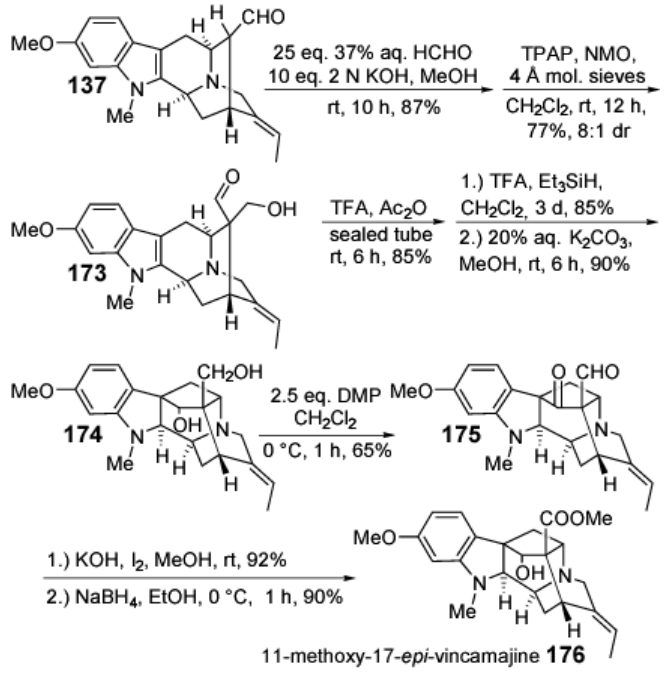
The Tollens reaction was also used by Cook and co-workers in their syntheses[66,67] of (–)-vincamajinine **172**, and (–)-11-methoxy-17-*epi*-vincamajine **176**. The synthesis of **172** (Scheme 53) also commenced with the transformation of *N*-methylvellosimine into the 1,3-diol **164**. To enable cyclisation to the ajmaline skeleton, a selective oxidation to a β-hydroxyaldehyde was needed. In the event, TPAP was able to selectively oxidise the less hindered hydroxymethyl group with diastereoselectivity > 10:1. Treatment of **168** with trifluoroacetic acid and acetic anhydride in a sealed tube effected the C7-C17 cyclisation, giving **169**, and then the unwanted C2-hydroxyl was reduced to give **170**. Completion of the synthesis of **172** (*via* **171**) required several sequential oxidations and reductions – all attempts to combine these steps resulted in a dramatic drop in yield. (–)-Vincamajinine **172** was obtained in 12% overall yield from D-tryptophan methyl ester.



Scheme 53.

The synthesis of (–)-11-methoxy-17-*epi*-vincamajine **176** (Scheme 54) was broadly similar to that of **172**, except that a ring-oxygenated precursor (*N*-methyl-16-*epi*-gardneral **137**) was employed. The Tollens reaction has been shown

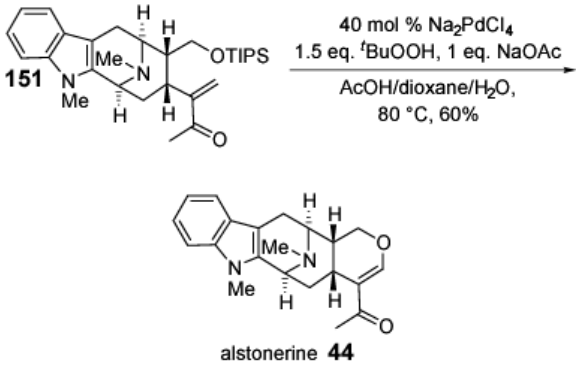
Scheme 54.



to be compatible with both C10 and C11 oxygenation.[65] (–)-11-Methoxy-17-*epi*-vincamajine **176** was obtained *via* **173**, **174** and **175** in an overall yield of 8% from 10-methoxy D-tryptophan ethyl ester **123**. Cook has also prepared[66] related compounds such as quebranchidine diol, epimeric at C17.

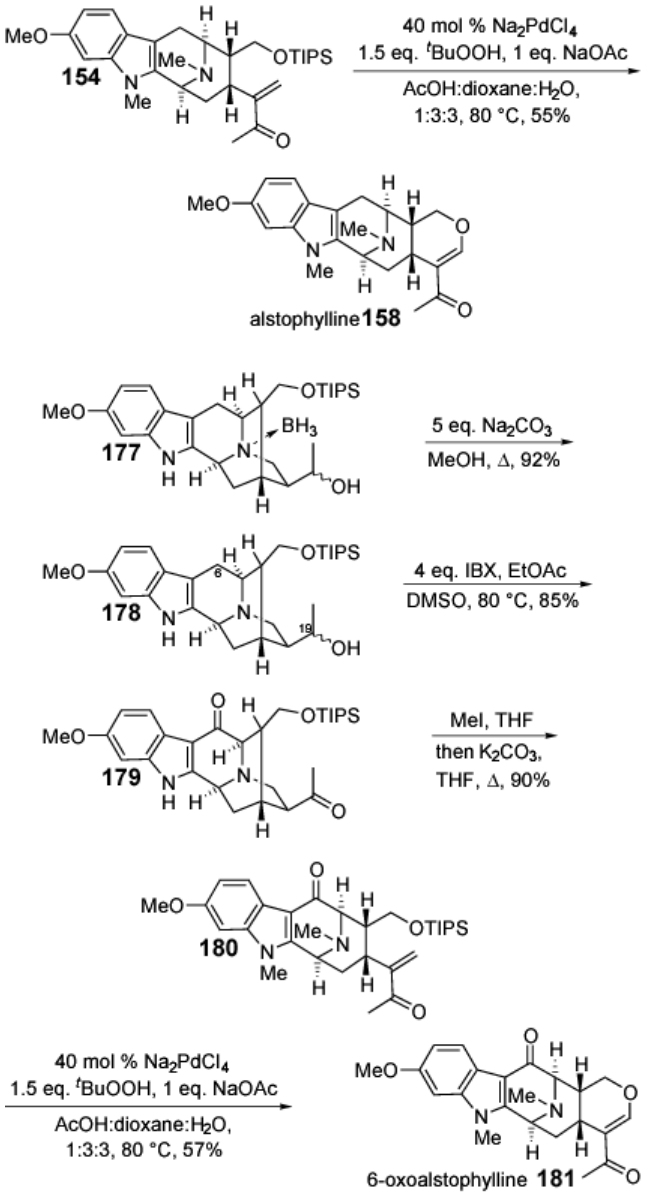
2.12. Modified Wacker oxidation: alstophylline, 6-oxoalstophylline, alstonerine and macralstonine

Cook has recently reported[68] the use of a modified Wacker protocol[69] to improve on the previous syntheses of the above-named alkaloids. For example, in the third generation synthesis of (–)-alstonerine, silylated macroline equivalent **151** (described in Section 2.9) undergoes deprotection and oxidative cyclisation directly to (–)-alstonerine **44** in a palladium-catalysed process employing ^{t}BuOOH as oxidant (Scheme 55). The yield of 60% is the result of optimisation work.



Scheme 55.

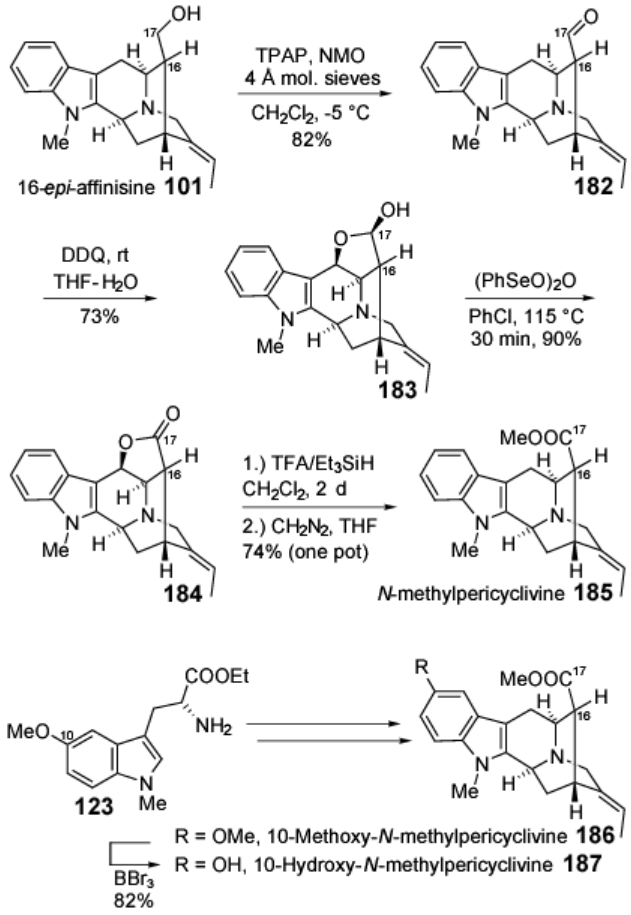
(–)-Alstonerine **44** was synthesised in 9% overall yield from D-tryptophan methyl ester. In a second-generation synthesis of (–)-alstophylline **158** (Scheme 56), the same protocol was applied to the corresponding 11-methoxymacroline equivalent **154**, affording **158** directly in 55% yield. (–)-Alstophylline **158** was obtained in 9% overall yield from 11-methoxy amino acid ester **135**. This improved synthesis of (–)-alstophylline also constituted a second-generation synthesis of macralstonine **159** (*c.f.* Section 2.9). Finally, to effect the first total synthesis of (+)-6-oxoalstophylline **181**, silylated sarpagan borane adduct **177** underwent N4-B bond scission to give **178**, and was then oxidised[70] with excess IBX to effect not only C19, but also C6, ketone formation. Tertiary amine **179** underwent Hofmann elimination as expected, giving **180**, and the modified Wacker protocol furnished (+)-6-oxoalstophylline in 10% overall yield from 11-methoxy amino acid ester **135**. The mechanism of the modified Wacker oxidation has not yet been fully elucidated.



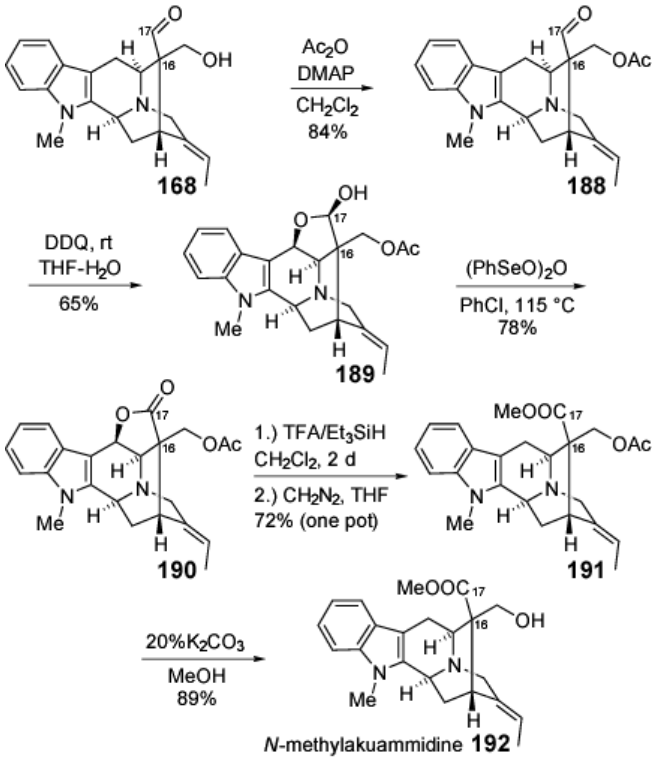
Scheme 56.

2.13. Lactol protection: 10-hydroxy-*N*-methylpericyclivine, 10-methoxy-*N*-methylpericyclivine, 12-methoxy-*N*-methylvoachalotine, *N*-methylakuammidine and *N*-methylpericyclivine

Certain of Cook's syntheses have been of sarpagine-related alkaloids that have required protection of C17. For instance, in the synthesis[71] of *N*-methylpericyclivine **185**, formation of the C17 ester was complicated by the fact that C16 epimerisation gave the more stable isomer, *N*-methyl-16-*epi*-pericyclivine **95**, under many ester-forming conditions. It was ascertained after experimentation that protection of the C17 aldehyde of **182** as a lactol (using the



DDQ methodology outlined in Section 2.3.2) permitted oxidation of C17 (in **183**) to the correct oxidation state (in **184**) with retention of the desired C16 configuration. Reductive deprotection of the lactone with Et_3SiH and TFA and *in-situ* esterification gave the desired *N*-methylpericyclivine **185** (10% overall yield from D-tryptophan methyl ester). A similar approach[71] starting from ring-oxygenated tryptophan derivative **123** afforded 10-methoxy-*N*-methylpericyclivine **186** (9% from **123**) and 10-hydroxy-*N*-methylpericyclivine **187** (7% from **123**), Scheme 57.



Scheme 57.

In the case of *N*-methylakuammidine[71] **192**, the configuration at the quaternary C16 was retained by the same protection strategy. In this instance, protection of the hydroxyl moiety in the final product as an acetate was also indicated (*via* **188**-**191**, Scheme 58). *N*-methylakuammidine **192** was synthesised in 6% yield from D-tryptophan.

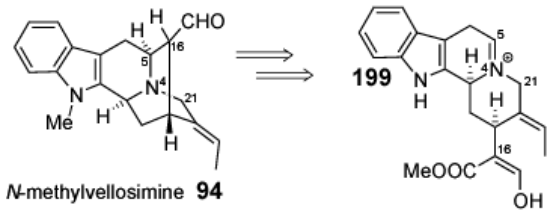
A similar protection strategy was adopted in Cook's recent synthesis[60] of 12-methoxy-*N*-methylvoachlotine **198**. In this instance, the protection was at a lower level of oxidation – as a cyclic ether, as opposed to a γ-lactol or lactone. 12-Methoxy-*N*-methylvellosimine **145** was subjected to the Tollens reaction as before to give **193**, and then to the sequence of transformations effecting the protection (**194**), transformation (**195** and **196**) and deprotection (**197**); quaternisation furnished 12-methoxy-*N*-methylvoachlotine **198** in 20% yield from **144**, Scheme 59.

Scheme 58.

Scheme 59.

3. Martin's Biomimetic Synthesis of (+)-*N*-Methylvellosimine

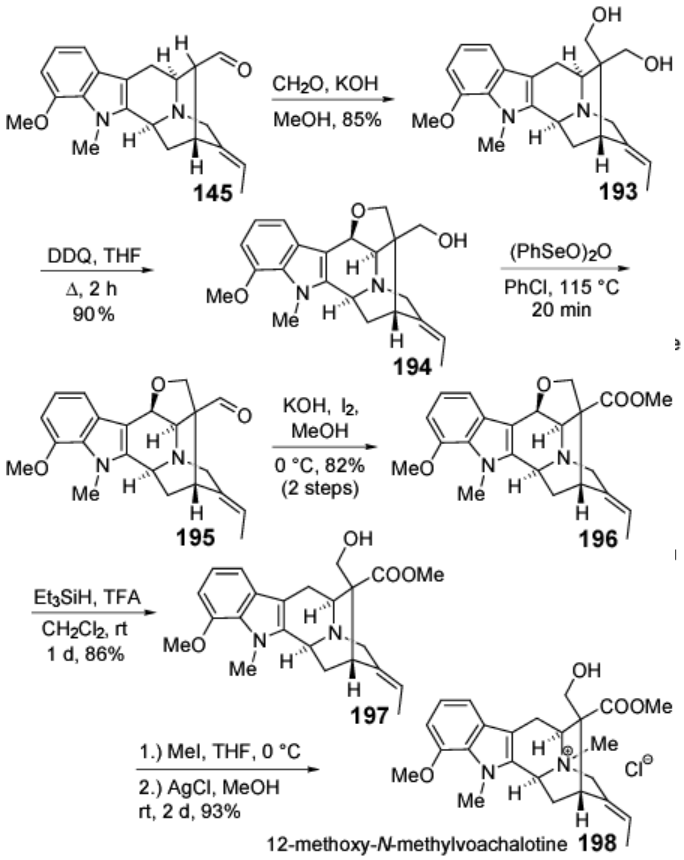
Martin *et al.* have reported[72] an enantiospecific total synthesis of *N*-methylvellosimine **94**, which differs fundamentally from that of Cook in that formation of the C5-C16 bond is the final C-C bond-forming event (**199**,



Scheme 60).

Scheme 60.

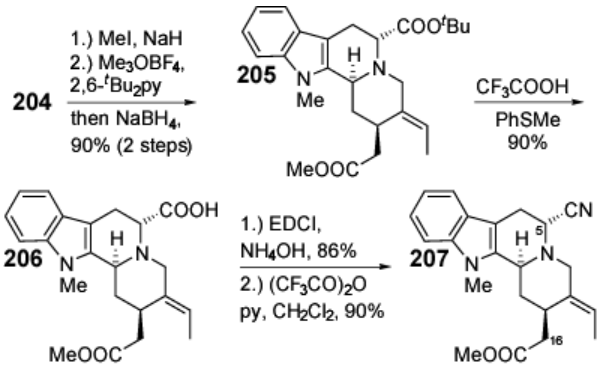
That such a reaction might occur in the biosynthesis of **94** was first proposed by van Tamelen,[73,74] a proposition supported by the subsequent report[75,76] of a biogenetic-type synthesis of ajmaline involving just such a transformation. Later, Lounasmaa *et al.* attempted the cyclisation of similar iminium ions, but with no success.[77] This led them to



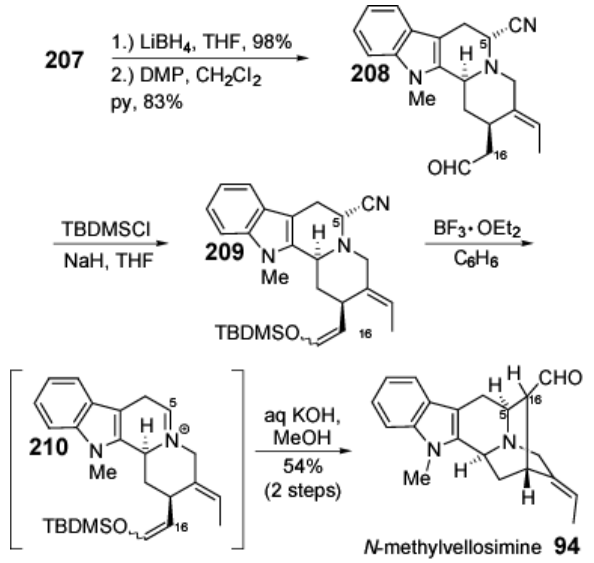
propose an alternative biosynthesis for the formation of the sarpagan skeleton, with C5-C16 bond formation as the *penultimate* skeletal bond-forming transformation and N4-C21 bond formation as the final cyclisation. Partly to discern which pathway was most likely to operate, Martin and co-workers undertook the synthesis outlined below.

Scheme 61.

Martin's synthesis (Scheme 61) commenced with the vinylogous Mannich reaction of dihydro-β-carboline **200** (derived from D-tryptophan and formic acid in 60% yield)

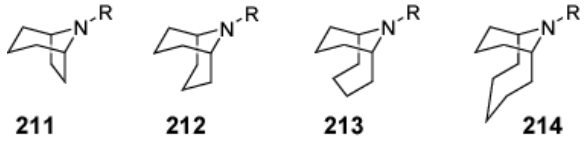


with silyl ketene acetal **201** to give tetrahydro-ß-carboline **202** with total diastereoselectivity. Introduction of the 4-carbon C18-21 fragment with diketene (and concomitant cyclising Michael addition) gave tetracycle **203**. Stepwise borohydride reduction and elimination gave α,β-unsaturated amide **204** as a single geometric isomer. N1-methylation, amide reduction (giving **205**) and selective ester hydrolysis gave the potential iminium precursor **206**. It was decided to employ an α-aminonitrile as the actual iminium precursor, as these were known to furnish iminium ions under mild conditions. α-Aminonitrile **207** was thus synthesised by introduction of an amide at the C5 position



and its subsequent dehydration (Scheme 62).

Scheme 62.



α-Aminonitrile **207** was subjected to imine-generating conditions, but no C5-C16 cyclisation was observed. This was taken to mean that the ester was insufficiently activating and so it was converted into the aldehyde **208**. This also was inert to cyclisation, but, upon formation of the corresponding silyl enol ether **209** and treatment with $BF_3{\cdot}OEt_2$, cyclisation to the sarpagan skeleton was observed (Scheme 63).

Scheme 63.

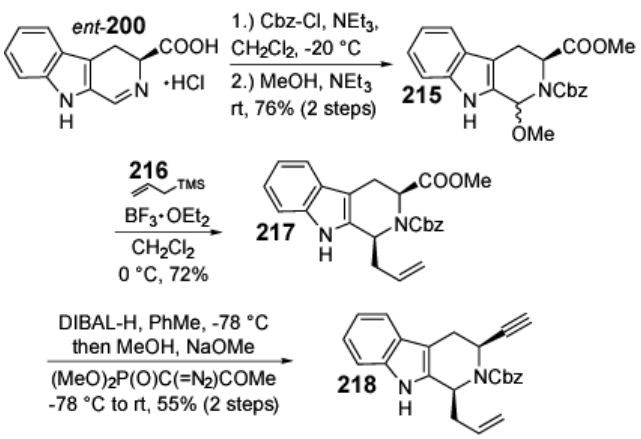
The target was obtained as an epimeric mixture (7:3 (+)-*N*-methylvellosimine:(+)-16-*epi*-*N*-methylvellosimine). As the desired natural epimer is the more thermodynamically stable, conversion into pure **94** was achieved by exposure of the mixture to aqueous KOH in MeOH. This elegant synthesis (7% overall yield from D-tryptophan) provides significant evidence for the feasibility of van Tamelen's original biogenetic pathway. Furthermore, it points to the possibility that the total synthesis of other sarpagine/ajmaline alkaloids might be *via*ble *via* such an iminium-induced cyclisation.

4. Martin's Olefin Metathesis Route to Azabicyclo[3.3.1]nonenes

Martin *et al*. have conducted an extensive study[78] on olefin metathesis as a method of accessing various azabicyclo[m.n.1] structures (m = 3-5, n = 2-3, with the nitrogen in the 1-atom bridge). Such structural motifs (**211**-**214**) are common in alkaloids (Scheme 64).

Scheme 64.

An indole-annulated azabicyclo[3.3.1] structure constitutes the tetracyclic skeleton of the macroline/sarpagine/ajmaline alkaloids and Martin and co-workers have been able to access this skeleton, as shown in Scheme 65.

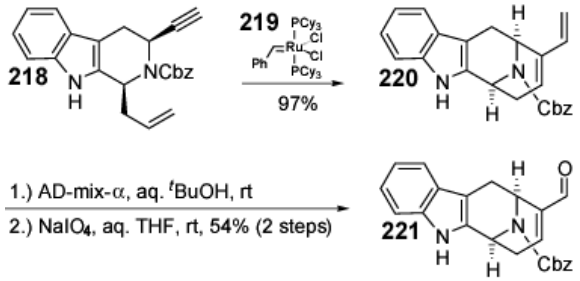


Scheme 65.

Starting this time from L-tryptophan, the dihydro-β-carboline *ent*-**200** (accessed in 63% yield) was *N*-protected before aminal formation with *in situ* esterification. The diastereoisomeric mixture **215** was treated with allyltrimethylsilane **216** and boron trifluoride etherate to afford C3,C5-*cis* tetrahydro-β-carboline **217** in a 5.5:1 diastereoisomeric ratio. The ester was then selectively reduced and the aldehyde reacted with the diazophosphonate shown to afford the alkyne in a one-pot procedure. This alkyne **218** underwent enyne metathesis (Scheme 66) with Grubbs' first-generation catalyst **219** to give tetracyclic diene **220** in essentially quantitative yield. The monosubstituted olefin of this diene was then selectively cleaved with AD-mix-α[79] and $NaIO_4$ to give α,β-unsaturated aldehyde **221**.

Scheme 66.

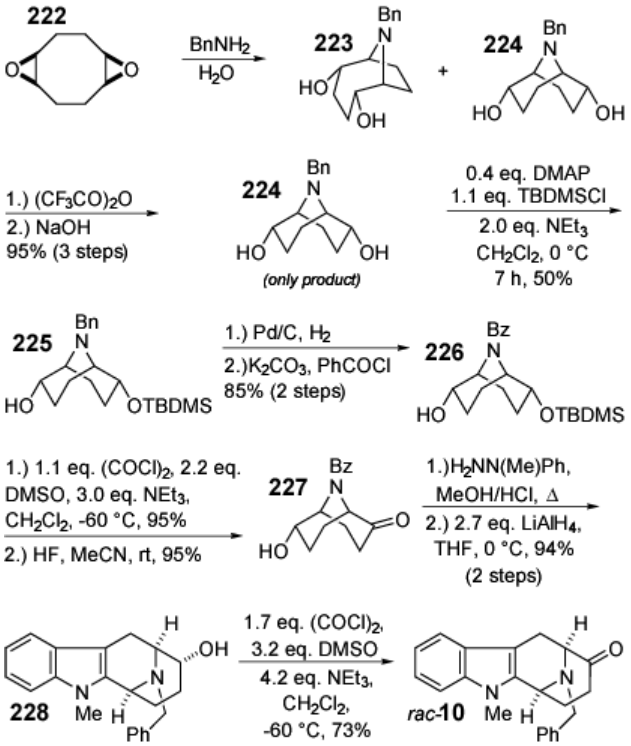
The α,β-unsaturated aldehyde **221** (10% yield from L-tryptophan) is a differentially protected form of the advanced intermediate **61** reported by Cook in the enantiospecific syntheses of macroline/sarpagine/ajmaline alkaloids, as detailed in Section 2. As such, this report from Martin constitutes a useful alternative approach to these



natural products, starting, as it does, from L-tryptophan.

5. Rassat's Synthesis of the Tetracyclic Ketone

In 2000, Rassat and co-workers reported[80,81] a synthesis of Cook's tetracyclic ketone intermediate **10** (summarized in Scheme 67). The crucial strategic difference in this approach is that formation of the [3.3.1]bicyclic skeleton occurs prior to the introduction of an indole.

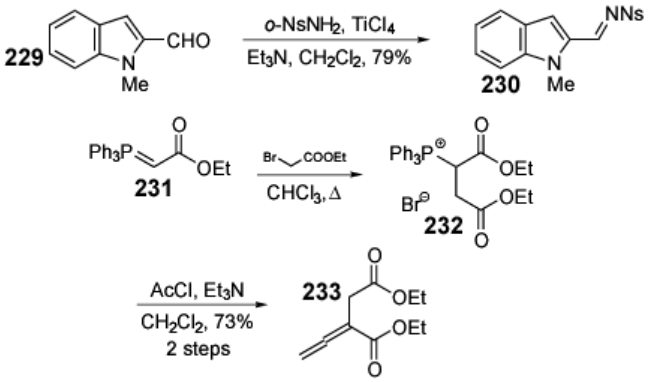


Scheme 67.

Transannular cyclisation of the bis(epoxide) starting material **222** with benzylamine led to a regioisomeric mixture of bicyclic structures. The unwanted [4.2.1]bicycle **223** may be converted into the desired [3.3.1]bicycle **224** under conditions of trifluoroacetate formation and subsequent hydrolysis. Selective monoprotection of the resultant diol to give **225** was followed by a protecting group swap, giving **226**. Oxidation to the ketone and deprotection of the other hydroxyl functionality led to the precursor **227** for Fischer indole synthesis of the tetracyclic core. This was effected in good yield with *N*-methyl-*N*-phenylhydrazine in acidic methanol at reflux overnight. Reduction to **228** regenerated the original *N*-benzyl protecting group and oxidation afforded the racemate of Cook's intermediate **10** in 25% overall yield.

6. Kwon's Formal Syntheses of (±)-Alstonerine and (±)-Macroline

Kwon and co-workers' formal syntheses[82] arose from their interest in phosphine-catalysed [4+2] annulations.[83] This key reaction occurred between an indolyl imine dienophile **230** (prepared from **229**) and a diene synthetic equivalent, the allenyl diester **233** (prepared from **231** *via* **232**). The synthesis of these two coupling partners is shown in Scheme 68.



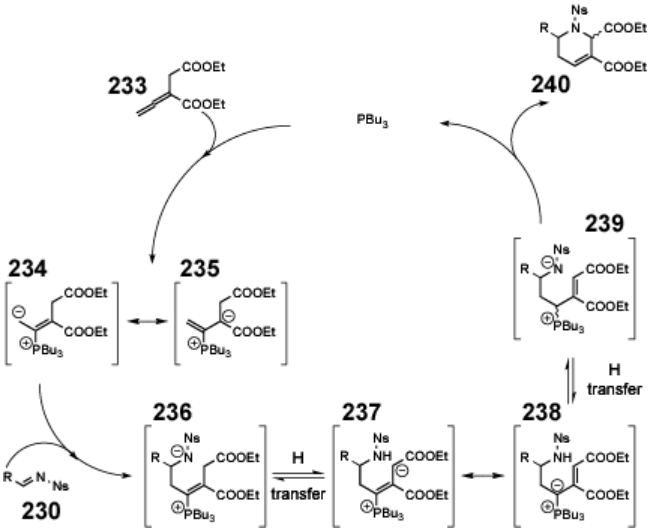
Scheme 68.

The cyclisation of **230** and **233** proceeded in 73% yield to give **241** as a 3:1 mixture of diastereoisomers. The proposed mechanism (believed to proceed *via* intermediates **234**-**240**) is shown in Scheme 69.

Under acidic conditions, the [4+2] product **241** underwent an intramolecular Friedel–Crafts acylation (Scheme 70) to give the tetracyclic macroline skeleton **242**. Thiolate-mediated N4-deprotection and subsequent Eschweiler–Clarke N4-methylation both proceeded in essentially quantitative yield to give **243**. $NaBH_4$ and ZnI_2 effected benzylic ketone reduction (along with formation of the N4-borane adduct, **244**; the N-B bond was cleaved by heating to reflux in EtOH). DIBAL-H ester reduction gave the tetracyclic allyl alcohol *rac*-**37**.

Scheme 69.

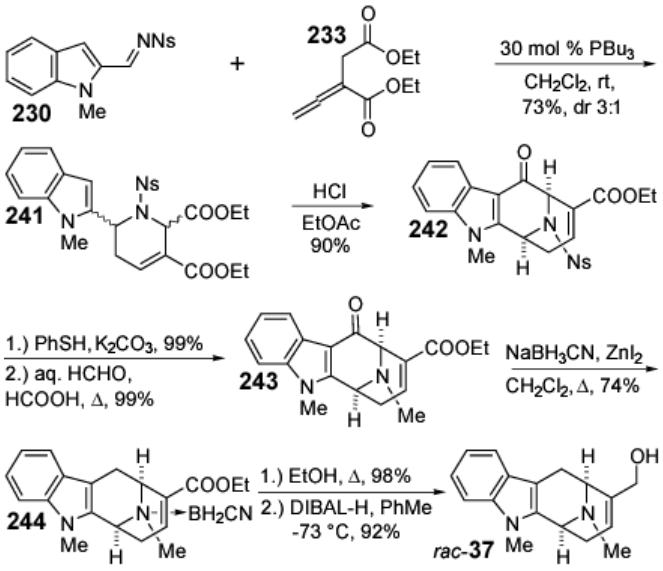
Racemic alcohol *rac*-**37** (31% yield, longest linear sequence) is an advanced intermediate in Cook's syntheses



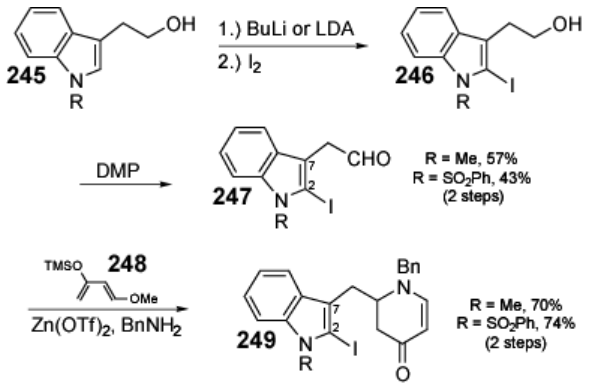
of alstonerine **44** and macroline **1** (see Sections 2.2 and 2.9).

Scheme 70.

7. Kuethe's Aza-Diels–Alder/Intramolecular Heck Approach

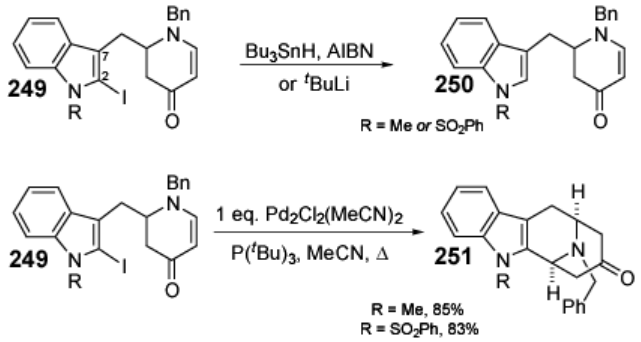


Kuethe and co-workers[84] have also adopted a [4+2] annulation strategy for construction of the tetracyclic macroline core. Adapting the work of Waldmann,[85] they employed Danishefsky's diene **248** with an imine derived from **245** (*via* **246** and **247**), the connectivity of which was different to that used by Martin, in that it was derived from an indole substituted at the C7-position, not the C2-position. The cyclisation is shown in Scheme 71.



Scheme 71.

Kuethe's group then attempted the synthesis of the desired tetracyclic system under conditions of both transmetallation and radical initiation. In both instances, however, the substrate **249** was simply deiodinated at the indolyl 2-position. The desired cyclisation was eventually effected



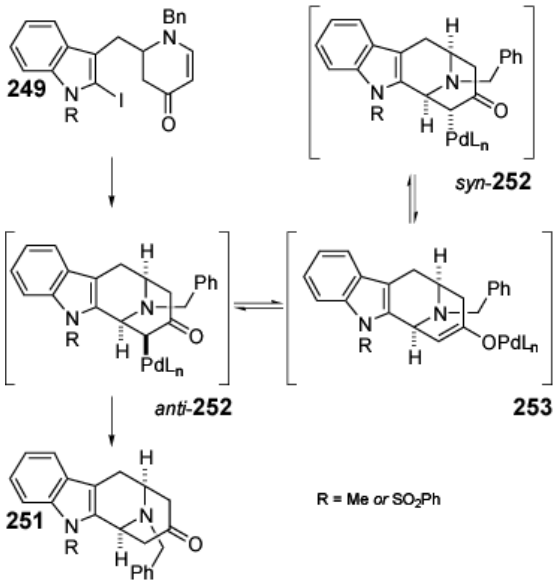
by the use of palladium, giving **251** (Scheme 72).

Scheme 72.

The reaction required stoichiometric amounts of Pd^{II} – rapid deposition of palladium black was observed during the course of the reaction. The inability of the reaction to go to completion under catalytic Heck conditions is presumed to arise from the lack of an appropriate β-hydrogen for elimination. The proposed intermediate *anti*-**252** (Scheme 73) has no β-hydrogen for *syn* elimination. Whilst isomerisation *via* a palladium enolate **253** is feasible,[86] *syn* elimination still does not occur, presumably since it would entail the formation of a high-energy anti-Bredt bridgehead olefin.

Attempts at performing the catalytic Heck reaction under reductive conditions led only to isolation of the deiodinated by-products **250**. When a modified Heck substrate **255** that contained additional β-hydrogens (the extra methyl group in **254** compared to **248**) was prepared, this smoothly underwent cyclisation with 10 mol% Pd^0 to give **256** (Scheme 74).

Scheme 73.



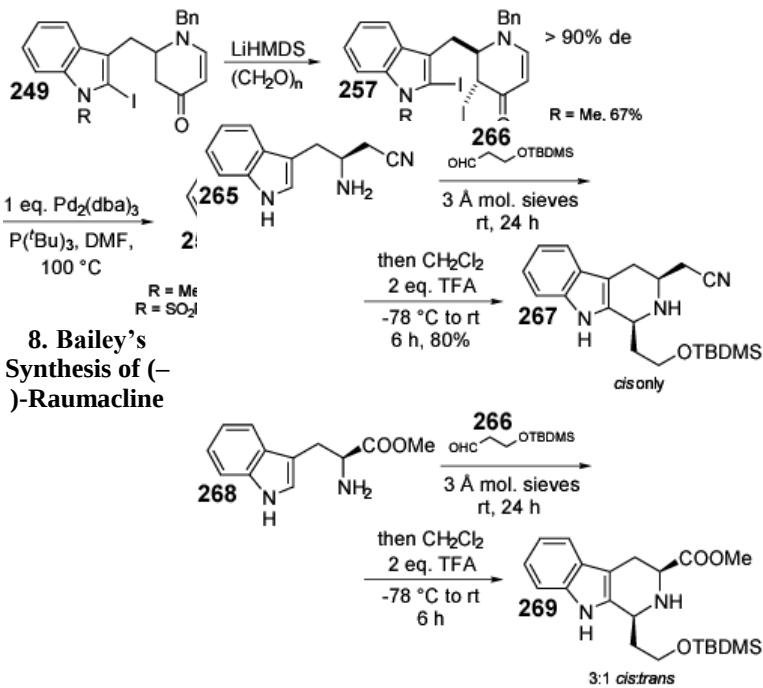
Many ajmaline/sarpagine alkaloids possess a hydroxymethyl group at the C16 position. In order to introduce such a moiety, **249** was hydroxymethylated to give **257** prior to palladium cyclisation, as before, to give **258**. Notably, appreciable amounts of α,β-unsaturated ketone **259** were isolated also. This is proposed to arise by elimination from the palladium enolate of type **253**. Whilst the use of stoichiometric amounts of palladium has obvious disadvantages, this entry to the tetracyclic macroline skeleton is novel and reasonably succinct (e.g. *N*-methyl-**258**, 5 steps, 9% yield, Scheme 75).

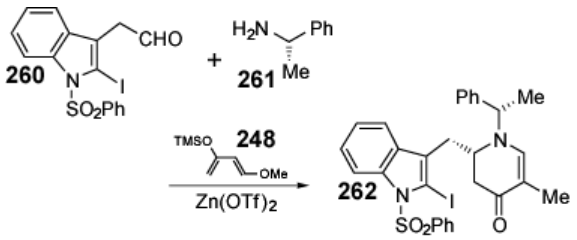
Scheme 74.

Scheme 75.

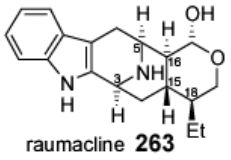
Efforts are currently under way to induce asymmetry[87] in the aza-Diels–Alder cyclisation by use of a chiral amine for imine formation. For example, the use of the imine derived from (*S*)-α-methylbenzylamine **261** and indolyl aldehyde **260** gave rise to dihydropyridone **262** in a diastereoisomeric ratio of 92:8 (Scheme 76).

Scheme 76.





Like Cook, Bailey and co-workers have made extensive study of the Pictet–Spengler reaction and have utilised it in previously reported formal syntheses of ajmaline, koumidine and suaveoline, amongst others.[88] Unlike Cook, Bailey's syntheses have as their core strategy the use of C3,C5-*cis*-specific Pictet–Spengler reactions. This permits the use of L-tryptophan to access various tetrahydro-β-carbolines having the correct configuration at C-3 and C-5 and this approach was used in Bailey's recent synthesis of raumacline[89] (**263**, Scheme 77). In contrast, Cook employs D-tryptophan in C3,C5-*trans*-specific Pictet–Spengler

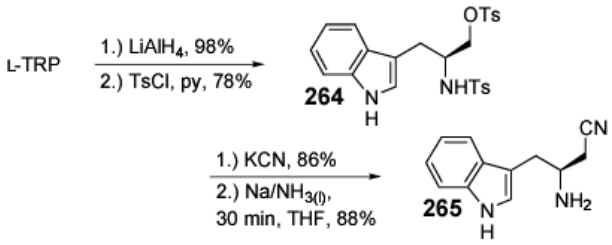


raumacline **263**

reactions, followed by selective epimerisation at C-5.

Scheme 77.

Bailey *et al.* employed cyanomethyltryptamine **265** as their Pictet–Spengler substrate.[90] It may be synthesised in 4 steps from the amino acid starting material on a large scale with no need for chromatography – the cyanosulfonamide made from **264** may be purified by crystallisation and the subsequent reductive desulfonylation has been optimised to provide pure **265** (Scheme 78).



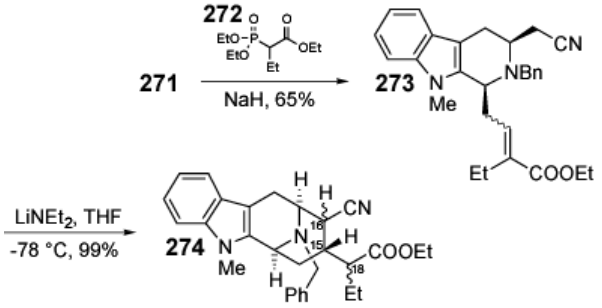
Scheme 78.

Pictet–Spengler cyclisation of **265** with a protected β-hydroxyaldehyde **266** gave C3,C5-*cis* tetrahydro-β-carboline **267** entirely stereoselectively. The factors that influence the selectivity had previously been studied[91] and it had been shown that in general, only for reactions of aryl aldehydes with tryptophan allyl ester was total C3,C5-*cis* selectivity observed. A C-3 aryl substituent would not have been synthetically useful in the context of raumacline, however. A two-carbon masked aldehyde equivalent was required at the C-3 position, and the use of the silylated hydroxyaldehyde in conjunction with the cyanomethyl group is both synthetically useful and *cis*-specific. Such a choice of substituents likely arose from extensive optimisation; for example, cyclisation of the same aldehyde **266** with L-tryptophan methyl ester **268** gave **269** with only 3:1 *cis*-selectivity (Scheme 79).

Scheme 79.

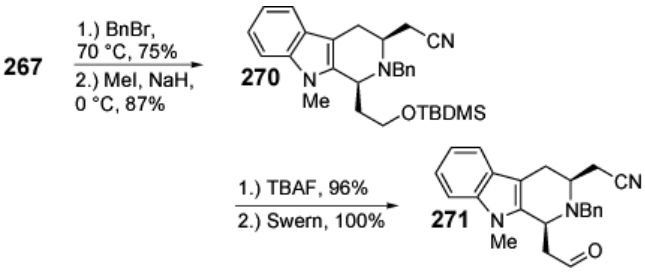
Once formed, tetrahydro-β-carboline **267** was N4-benzylated and N1-methylated without complication, giving **270**. It is probably significant that the Pictet–Spengler reaction was performed on the N1,N4-unsubstituted system; Cook has observed that an N4-benzyl substituent (or any bulky substituent) enhances C3,C5-*trans* selectivity in the cyclisation. Hydroxyl deprotection and oxidation to **271** were routine (Scheme 80).

Scheme 80.



Scheme 81.

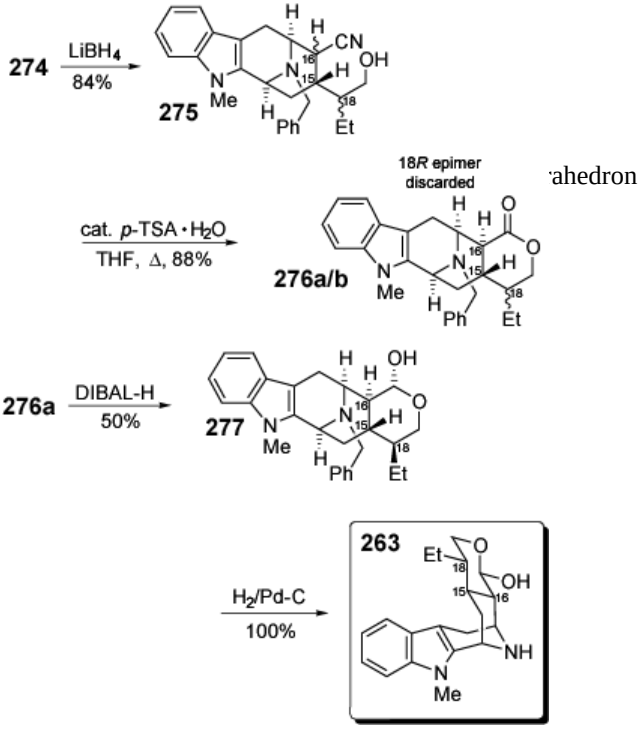
A Horner–Wadsworth–Emmons reaction with **272** furnished **273** (5:3 *E*:*Z*), the substrate for intramolecular Michael cyclisation to the tetracycle. This was induced with $LiNEt_2$, giving **274** as an inseparable mixture of diastereoisomers. C-15 was found to have entirely *R*



configuration as desired and C-16 was found to be 4:1 *S*:*R*. No selectivity was observed at C-18 (1:1 *S*:*R*). Bailey makes no comment relating the C-18 stereochemistry to olefin geometry or otherwise (Scheme 81).

Scheme 82.

After reduction, heating the resultant diastereoisomeric mixture **275** to reflux with catalytic toluene-4-sulfonic acid hydrate in THF gave a mixture of two lactones **276a/b**, diastereoisomeric at C-18. Gratifyingly, both C-16 epimers had been transformed only into (16*S*) lactones **276a/b**. Presumably the (16*R*) epimer of **275** had initially cyclised to the *cis*-decalin, before base-induced epimerisation to the *trans*-decalin structure. That the *trans*-decalin would be the lower-energy configuration may be seen from the predicted 3D structure of (–)-raumacline (Scheme 82), where the all-equatorial conformation is visible. The C-18 epimeric lactones were separated by chromatography and the isomer having the correct (18*S*) configuration (**276a**) underwent DIBAL reduction to introduce the lactol **277** (correctly



configured) and hydrogenolytic debenzylation to afford (–)-raumacline **263** (Scheme 82).

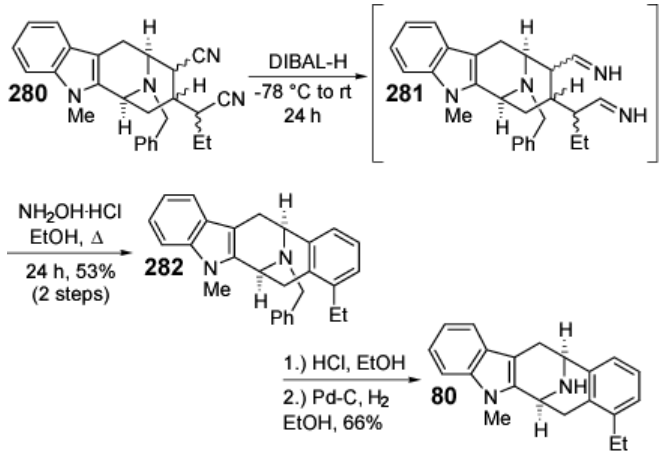
The difficulty in exerting control over the C-18 stereochemistry is regrettable, but, nevertheless, in this synthesis of (–)-raumacline (7% overall yield from L-tryptophan), five of the six stereocentres have been effectively controlled, a notable achievement and a significant improvement on previous approaches.

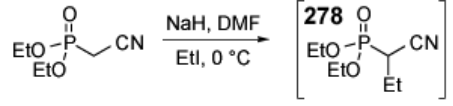
9. Bailey's Synthesis of (–)-Suaveoline

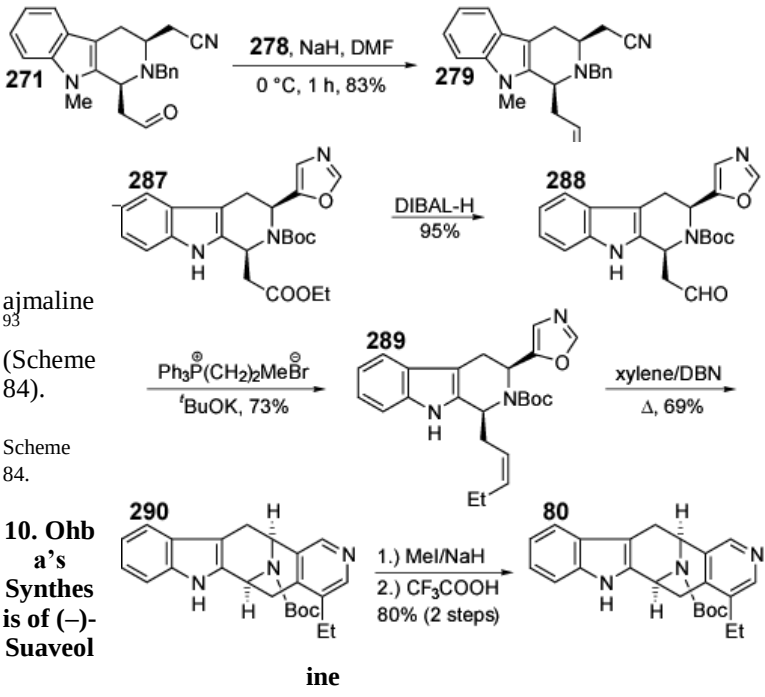
In addition to the earlier reported formal syntheses[88] of suaveoline and ajmaline, Bailey and co-workers have made many and varied additional contributions[92] to the field. These have culminated in a recent total synthesis of suaveoline.[93] The synthesis employs the same *cis*-selective Pictet–Spengler cyclisation described in Section 8, but in this instance, cyanoaldehyde **271** was homologated to an unsaturated bis(nitrile) species **279** by means of a Horner–Wadsworth–Emmons reaction. The phosphonate **278** was prepared by *in-situ* alkylation with ethyl iodide. A vinylogous Thorpe cyclisation was then effected, giving the tetracyclic intermediate **280** (Scheme 83).

Scheme 83.

Tetracycle **280** was isolated as a mixture of diastereoisomers, all of which were suitable for further elaboration to suaveoline. Completion of the synthesis was by DIBAL-mediated reduction of **280** to an intermediate diimine **281**. This was treated with hydroxylamine hydrochloride in ethanol to effect formation of pyridine **282**. N4-Deprotection gave suaveoline **80** (6% from L-tryptophan), idenitical with both the natural product and a sample of semisynthetic suaveoline prepared from





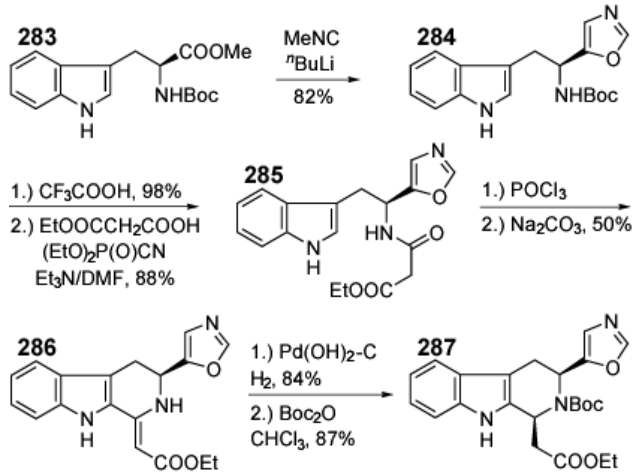


ajmaline[93] (Scheme 84).

Scheme 84.

10. Ohba's Synthesis of (–)-Suaveoline

The total synthesis of (–)-suaveoline reported by Ohba and co-workers[94] arose from their interest in oxazole–olefin



Diels–Alder reactions as a route to annulated pyridines. Formation of oxazole **284** from N4-Boc-protected L-tryptophan methyl ester **283** occurred without erosion of ee according to their previously reported methodology.[95] Temporary removal of the protecting group was necessary for *N*-acylation (giving **285**), Bischler–Napieralski reaction (6 days in neat $POCl_3$, giving **286**) and stereoselective hydrogenation (Scheme 85).

Scheme 85.

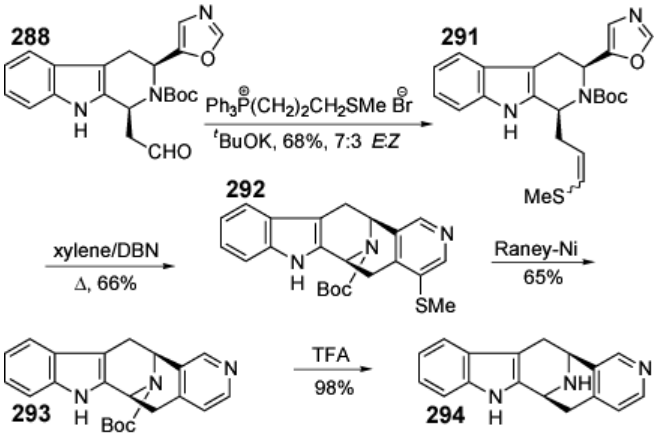
Upon re-introduction of the Boc group to give **287**, a chemoselective ester to aldehyde reduction was effected followed by Wittig reaction to introduce the ethyl sidechain. The IMDA reaction of **289** was found to work best by heating in xylene at reflux, with addition of 1,5-diazabicyclo[4.3.0]non-5-ene (suggested simply to be a scavenger for H_2O), giving pyridine **290** in 69% yield. N1-Methylation and N4-deprotection afforded (–)-suaveoline **80** in 10% yield from **283**. The route disclosed above is radically different from those of Bailey and Cook – instead

of relying on a Pictet–Spengler reaction to install the crucial tetrahydro-β-carboline stereochemistry, Ohba employs a diastereoselective reduction. Whilst the synthesis was most likely conceived primarily as a showcase for the pyridine-forming IMDA reaction, the aforementioned diastereoselective reduction may be of use for the synthesis of further members of the macroline/sarpagine/ajmaline indole class. It is noteworthy that, in this succinct synthesis, N1-protection was unnecessary (Scheme 86).

Scheme 86.

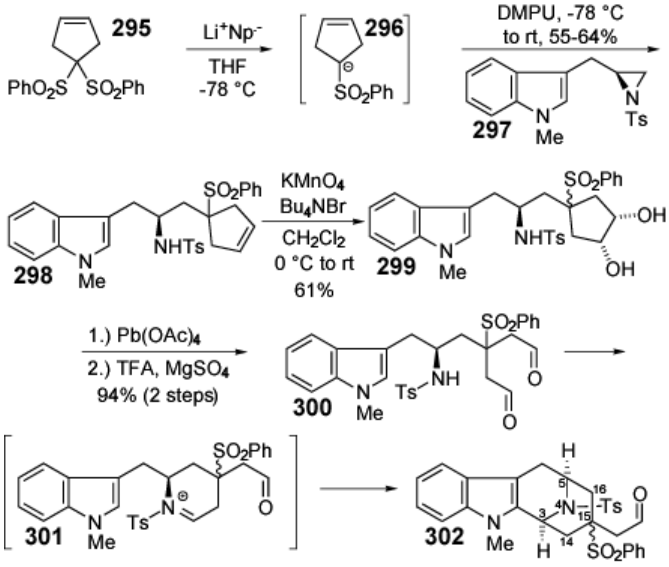
11. Ohba's Synthesis of 1-Demethyl-20-deethylsuaveoline

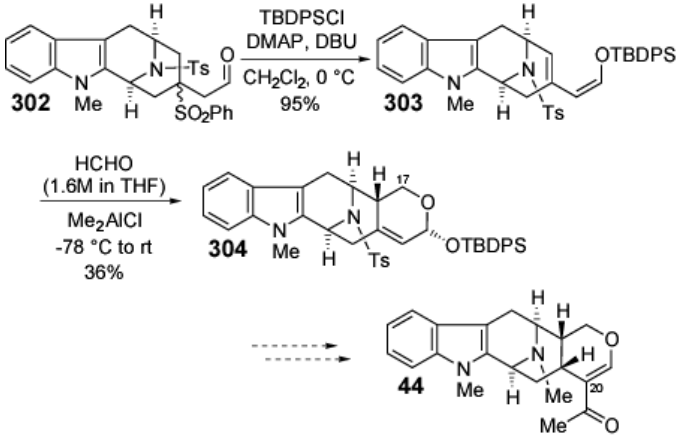
In 1996, Batista *et al.* isolated sellowiine, a macroline-related alkaloid, from the leaves of *Rauvolfia sellowii*.[96,97] For this natural product, they proposed the structure 1-demethyl-20-deethylsuaveoline **294**. The methodology of Ohba and co-workers was ideally suited to the synthesis of this structure and they were able to achieve a total synthesis[98] (Scheme 87).



Scheme 87.

Elaboration of aldehyde **288** was by a Wittig reaction to introduce a vinyl sulfide sidechain (it was found that a terminal olefin was not able to undergo the intramolecular Diels–Alder reaction). Thus the removable thiomethyl group was used instead, and the IMDA reaction of **291** gave pyridine **292** in good yield. Removal of the thiomethyl group from **292** by reduction with Raney-nickel (giving **293**) and trifluoroacetic acid-induced N4-deprotection gave





1-demethyl-20-deethylsuaveoline **294** (7% yield from N4-Boc L-tryptophan methyl ester). The spectroscopic data recorded by Ohba and co-workers for **294** did not correlate with those reported for sellowiine by Batista; the chemistry of sellowiine remains incomplete, therefore.

12. Craig's Approach to (–)-Alstonerine

Craig and co-workers have recently reported[99] the results of their studies on the syntheses of (–)-alstonerine **44** by an aziridine-based approach. Using methodology reported by Mioskowski,[100] they were able to generate anion **296** by reductive desulfonylation of bis(sulfone) **295**. This in turn was added to L-tryptophan-derived aziridine **297** to give **298**. The cyclopentene in **298** was employed as a dialdehyde surrogate; in order that it could be unmasked, a selective oxidation of the olefin in the presence of the indole was necessary. After optimisation, this was found to be *via*ble with tetra-*n*-butylammonium permanganate in CH_2Cl_2, giving 2**99**. Subsequent diol cleavage gave dialdehyde **300**, which underwent acid-induced Pictet–Spengler cyclisation *via* **301** to tetracyclic monoaldehyde **302** as a mixture of diastereoisomers (Scheme 88).

Scheme 88.

Craig's use of the Pictet–Spengler reaction is strategically different from Cook's or Bailey's. In Bailey's syntheses, *cis* selectivity was achieved in the Pictet–Spengler reaction by careful choice of reaction partners. In the current work, the tetrahydro-β-carboline geometry was formed exclusively *cis*, due to the cyclic nature of the iminium intermediate. This reversal of the order of events (formation of the C3-N4-C5-C16-C15-C14 ring prior to this *intramolecular* Pictet–Spengler cyclisation) neatly avoids stereochemical ambiguity in the cyclisation step. Monoaldehyde **302** was further elaborated by sulfone elimination and vinylogous silyl enol ether formation. The geometry shown for **303** was observed exclusively. Introduction of C17 was effected by the use of an unusual hetero-Diels–Alder reaction of formaldehyde. Monomeric formaldehyde, generated by a modified version of the Schlosser protocol,[101] was reacted with **303** under conditions of Lewis acid catalysis to give advanced pentacyclic intermediate **304** (9% from L-tryptophan). It can be seen that introduction of a pendant 2-carbon fragment at C20 would permit access to the complete alstonerine skeleton (Scheme 89).

Scheme 89.

13. Conclusions and Future Prospects

The chemistry detailed herein shows that considerable advances have recently been made in the field of sarpagine/macroline/ajmaline indole alkaloids since the field was last reviewed. The Pictet–Spengler reaction remains a key strategic transformation for the synthesis of molecules of this class, as evidenced by the work of Cook, Bailey and Craig. Nevertheless, a diverse array of other reaction classes have been deployed to access the targets in question. In particular, Cook's use of a common late-stage tetracyclic intermediate has allowed access to a large variety of natural products by use of varied transformations for the final elaborations. It is anticipated that further advances in the chemistry of macroline/sarpagine/ajmaline indole alkaloids will be reported in due course by many of the laboratories from which the work reviewed here originated.

Acknowledgements

The author would like to thank Professor Donald Craig and Dr Christopher J. T. Hyland for encouragement and helpful suggestions.

Biographical Sketch

Simon E. Lewis was born in London, UK in 1978. He received his MSci degree in 2001 from Imperial College, London, where he earned the SmithKline Beecham award for excellence in organic chemistry and was jointly awarded the Neil Arnott prize. After a short period with GlaxoSmithKline, he returned to Imperial College in 2002 where he was the beneficiary of a generous Pfizer CASE scholarship. He pursued his doctoral studies under the supervision of Professor Donald Craig, on the decarboxylative Ireland–Claisen rearrangement and its application to the synthesis of suaveoline. In 2006 he joined the group of Professor Andrew G. Myers at Harvard University where he is currently working on the synthesis of tetracycline antibiotics.

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